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Electrochemical dearomative dihydroxylation and hydroxycyclization of indoles

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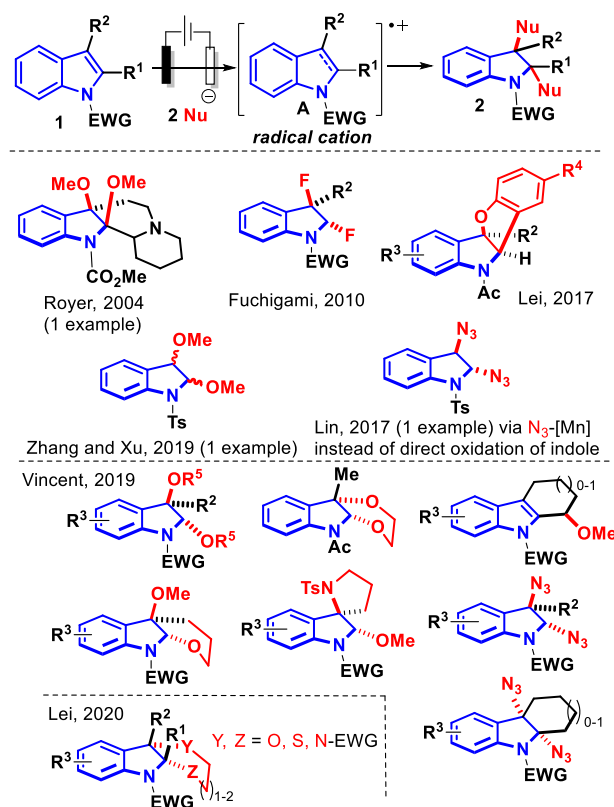
Supporting information for this article is available on the WWW under <http://dx.doi.org/10.1002/adsc.201#####>.

Abstract. We describe a simple and sustainable MgBr_2 -mediated electrochemical dearomative dihydroxylation and hydroxycyclization reactions of indoles with water. MgBr_2 is used in substoichiometric amount and acts as an electrolyte and potentially as a redox mediator to indirectly oxidize the indole nucleus into a bromonium ion which is involved in the aforementioned reactions.

Keywords: Electrochemistry; Indole; Dearomatization; Dihydroxylation; Electrocatalyst

In the last decade, the resurgence of electrochemistry^[1] contributed to an upsurge of oxidative vicinal difunctionalization methods of alkenes in sustainable conditions.^[2] The related electrochemical dearomative 1,2-difunctionalization of (hetero)arenes and in particular indoles has been less studied.^[3-8] The dearomatization of indole, for which we have been interested for almost a decade,^[9,10] generates three dimensional indolines of potential biological relevance.^[11] In few cases, dearomative electrolysis could be performed from an N-H indole substrate^[6] as it was demonstrated by Harran during the 60 gram-scale synthesis of the benzofuroindoline core of DZ-2384, a highly potent antitumoral agent inspired by the natural product diazonamide A.^[6b] However, most electrochemical methods to achieve this transformation rely on the generation of a radical cation **A** via the direct anodic oxidation of the indole nucleus **1** bearing an electron-withdrawing group on the nitrogen to deliver indolines **2**.^[7,8] According to this concept, Royer reported, in 2004, one example of the dearomative dimethoxylation of a β -tetrahydrocarboline.^[7a] One example of the dimethoxylation of the 2,3-unsubstituted N-Ts indole was latter reported by Zhang and Xu.^[7d] The 2,3-difluorination of indoles was described by Fuchigami in 2010.^[7b] More recently, Lei implemented in electrochemical conditions the oxidative coupling between N-Ac indoles and phenols^[7c] that we previously described in presence of FeCl_3 and DDQ.^[10b] It should also be noted that, Lin reported one

example of the diazidation of N-Ts indole via the formation of a N_3 -[Mn] intermediate which adds onto the indole nucleus.^[5a]

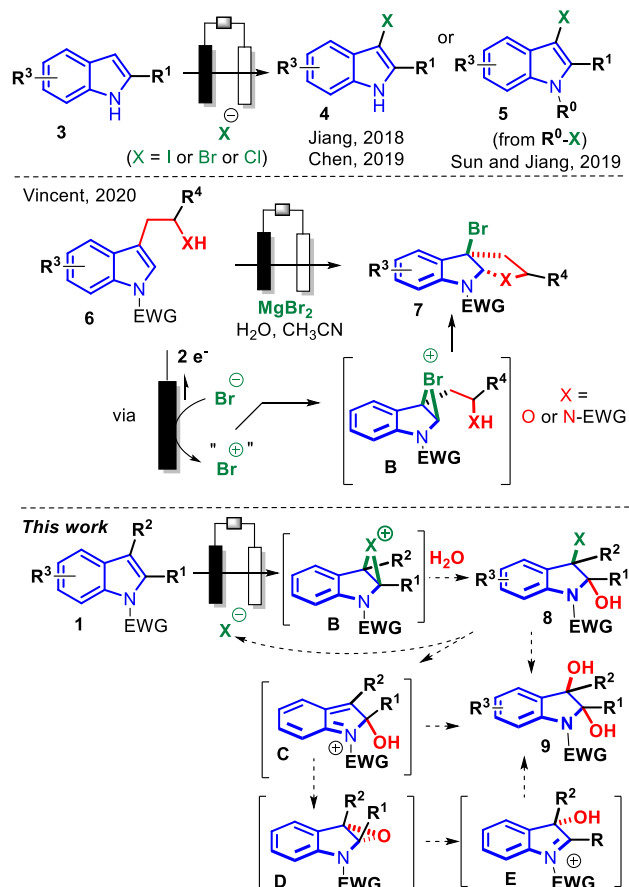


Scheme 1. Direct electrochemical dearomatization of N-EWG indoles.

In this context, we recently published a general dearomative difunctionalization of indoles N-substituted by an electron-withdrawing group in galvanostatic conditions (Scheme 1).^[8] In presence of alcohols, including ethylene glycol, 2,3-dialkoxylation occurred. In the case of 2,3-substituted indoles, the dimethoxylated indolines spontaneously evolved into α -methoxyindoles via elimination of methanol. In presence of an oxygenated or nitrogenated nucleophile

on the C3-substituent with a three carbon-linker, methoxycyclization was observed. Finally, the use of TMS azide as nucleophile resulted in the dearomatic 2,3-diazidation of indoles. Few months later, Lei described electrochemical dearomatic annulation reactions of indoles with diols and other O, N or S-containing bisnucleophiles.^[7e]

In contrast to the direct anodic oxidation of the indole nucleus, we very recently performed an indirect electrochemical dearomatization of indole derivatives (Scheme 2). Recognising that, like several other arenes and unsaturated substrates,^[12] 3-unsubstituted indoles **3** could be halogenated into **4** or **5** by electrolysis in presence of halides,^[13] we achieved the MgBr₂-mediated conversion of tryptophol, tryptamine and tryptophan derivatives **6** into bromofuranoindolines and bromopyrroloindolines **7** without the need of an additional electrolyte.^[14] In this process, MgBr₂ is presumably oxidized at the anode into an electrophilic bromine reagent which could react with the indole nucleus to form bromonium ion **B** which is then intramolecularly intercepted by the oxygen or nitrogen nucleophile on the C3-substituent to deliver **7**. A parallel could be drawn with the work of Tong who performed a similar process via the *in-situ* oxidation of halides with oxone in order to limit the generation of organic by-products or the use of toxic reagents.^[15]

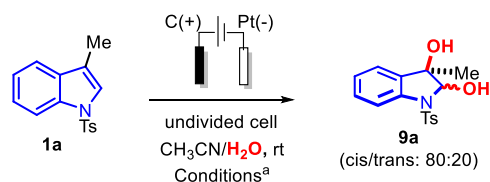


Scheme 2. Halide-mediated electrochemical dearomatization of indoles.

The purpose of the present report is to study the reactivity of other indole substrates without a pendant nucleophilic entity at the C3-position in electrochemical conditions with halide salts. We wondered if, in presence of a nucleophile such as water, the halonium ion **B** would deliver 2-hydroxy,3-haloindoline **8**. Alternatively, the halide of the latter could be displaced by a second molecule of water by direct S_N2 or via extended imminium **C** or via epoxide **D** and 3-hydroxyindolenium **E** in order to form the dihydroxyindoline **9**. In this case, the bromide ion would be regenerated and could act as a redox mediator in sub-stoichiometric amounts. It should be noted that halides are known electrocatalysts in the context of oxidative coupling reactions.^[16]

Consequently, we started to study the electrochemical dearomatization of N-Ts indole **1a** in water as a co-solvent with acetonitrile in an undivided cell with a graphite anode and a platinum cathode (Table 1).

Table 1. Optimization of the electrochemical dihydroxylation of **1a**.

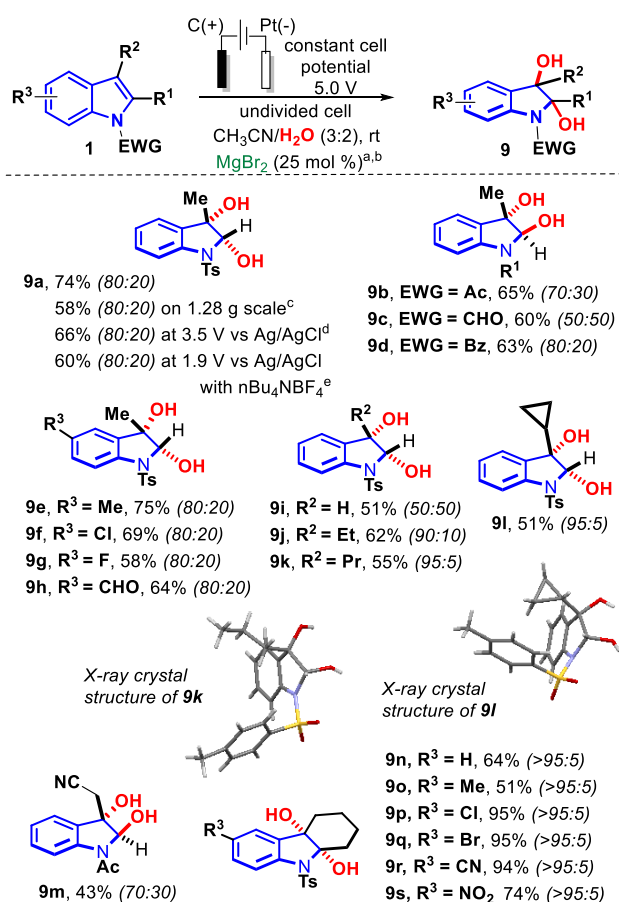


Entry	Additive (equiv.)	Current and cell potential ^b	CH ₃ CN/H ₂ O	Yield 9a ^c
1	Bu ₄ NBF ₄ (1)	9 mA/cm ²	4/1	49 %
2	Bu ₄ NBF ₄ (1)	9 mA/cm ²	3/2	50 %
3	MgCl ₂ (1)	9 mA/cm ²	4/1	34 %
4	NaCl (1)	9 mA/cm ²	4/1	28 %
5	MgBr ₂ (1)	9 mA/cm ²	4/1	47 %
6	NaBr (1)	9 mA/cm ²	4/1	33 %
7	KBr (1)	9 mA/cm ²	4/1	34 %
8	Bu ₄ NBr (1)	9 mA/cm ²	4/1	11 %
9	MgI ₂ (1)	9 mA/cm ²	4/1	NR
10	NaI (1)	9 mA/cm ²	4/1	NR
11	MgBr ₂ (0.25)	9 mA/cm ²	4/1	60 %
12	MgBr ₂ (0.25)	4.5 V	4/1	60 %
13	MgBr ₂ (0.25)	5 V	4/1	71 %
14	MgBr ₂ (0.25)	6 V	4/1	64 %
15	MgBr ₂ (0.25)	5 V	3/2	74 %

^a) Undivided cell, graphite-SK50 anode (1.4 cm x 0.8 cm x 0.2 cm submerged), platinum plated cathode (1.4 cm x 0.8 cm x 0.2 cm submerged), **1a** (0.2 mmol), additive, 5 mL of CH₃CN/H₂O, room temperature; ^b) between the two electrodes; ^c) Isolated yield.

In our previous reported conditions of direct anodic oxidation of **1a** at a constant current of 9 mA.cm⁻¹ with nBu₄NBF₄ as electrolyte, dihydroxyindoline **9a** was obtained in a moderate yield (entries 1,2).^[17] Replacing the electrolyte by a halide salt also delivered dihydroxyindoline **9a** without the observation of 2-

hydroxy-3-haloindoline **8a** (entries 3-8). Among the chlorides (entries 3,4), bromides (entries 4-8) and iodides (entries 9,10) which were evaluated, MgBr_2 proved to be the more promising redox mediator (entry 5). We observed the bromination of the benzene ring of **9a** as a side reaction. Therefore, decreasing the load of MgBr_2 from one equivalent to 0.25 equivalent led to an increase of the yield to 60% (entry 11). Conducting the electrolysis in potentiostatic conditions (entries 12-14) instead of galvanostatic conditions led to an improved yield (71%) at a constant potential of 5V between the two electrodes (entry 13). Finally, a slight increase of the yield to 74% could be obtained, as a 4:1 diastereoisomeric ratio in favour of the *cis* diastereoisomer, with a higher concentration of water (entry 15). Very usefully, in addition to potentially be a redox mediator, MgBr_2 also acts as an electrolyte.



Scheme 3. MgBr_2 -mediated electrochemical dearomative dihydroxylation of indoles. ^{a)} Undivided cell, graphite-SK50 anode (1.4 cm x 0.8 cm x 0.2 cm submerged), platinum plated cathode (1.4 cm x 0.8 cm x 0.2 cm submerged), constant potential of 5 V between the electrodes, **1** (0.2 mmol), MgBr_2 (0.05 mmol), $\text{CH}_3\text{CN}/\text{H}_2\text{O}$ (3 mL/2 mL), room temperature; ^{b)} isolated yields (diastereomeric ratio of the major isomer as drawn) are indicated; ^{c)} anode (3.4 cm x 0.8 cm x 0.2 cm submerged), cathode (3.4 cm x 0.8 cm x 0.2 cm submerged), **1** (4.5 mmol), MgBr_2 (1.125 mmol), $\text{CH}_3\text{CN}/\text{H}_2\text{O}$ (10 mL/6 mL); ^{d)} constant potential of 3.5 V at the anode vs an Ag/AgCl (3M aq. KCl) ref electrode; ^{e)} constant potential of 1.9 V at the anode vs an Ag/AgCl (3M

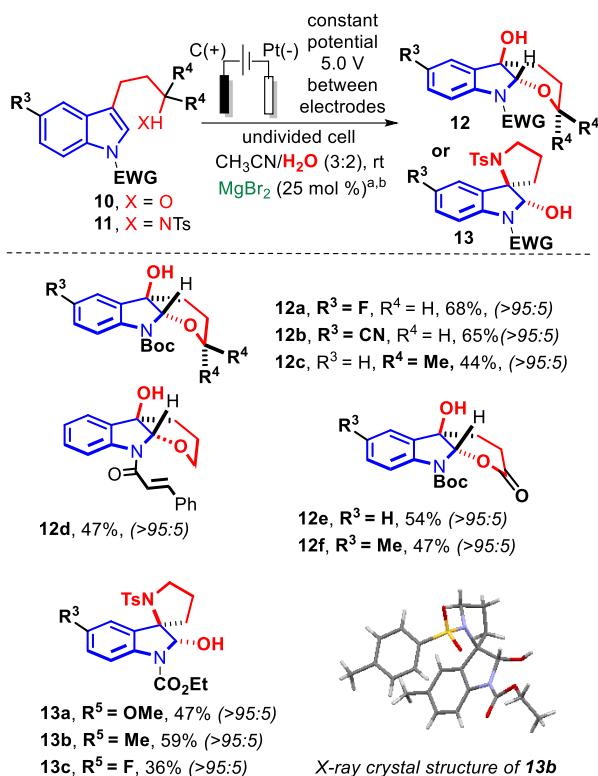
aq. KCl) ref electrode when $n\text{Bu}_4\text{NBF}_4$ (0.2 mmol) was added to the reaction mixture.

The synthesis of **9a** could be conducted on a gram scale (Scheme 3). We also performed successfully the electrolysis with a constant potential of 3.5 V at the anode vs an Ag/AgCl reference electrode. In this case, 3.5 V is unlikely the anode potential due to the probable high resistance of the reaction mixture. Therefore, to decrease the resistance of the solution, $n\text{Bu}_4\text{NBF}_4$ was added as an additional supporting electrolyte and a 60% yield of **9a** was obtained at 1.9 V vs Ag/AgCl with 0.25 equiv. of MgBr_2 .

Subsequently, we studied the scope of this MgBr_2 -mediated electrochemical dihydroxylation reaction at a constant cell potential of 5V in order to have a simple reaction set-up (Scheme 3). Switching the tosyl group born by the nitrogen of the indole to acyl groups such as acetyl, formyl and benzoyl yielded indolines **9b-d** but with the *trans* isomer as the major product.^[17d] The diastereoselectivity of this dihydroxylation of indoles appears to be controlled by the indolic nitrogen substituent. At this point, we decided to continue our investigation with a tosyl as the electron-withdrawing group on the nitrogen in most cases.^[18] The substitution on the benzene part of the indole proved to be tolerant to both electron-donating groups, halogens and electron-withdrawing groups with the formation of indolines **9e-h** with the *cis* isomer as the major product. A sensitive aldehyde is compatible in these conditions as demonstrated by the synthesis of dihydroxyindoline **9h**. 2,3-Unsubstituted-N-Ts-indole was also a competent substrate which delivered indoline **9i**. The *cis*-dearomative dihydroxylation of N-Ts indoles proceeded well with various substituents at the C3-position such as alkyl groups (**9j-l**).^[19] 3-Cyclopropyl-indoline **9l** was obtained with only minor amounts of the opening of the cyclopropyl ring.^[19] A nitrile could also be present on the C3-alkyl side chain to deliver **9m** without hydrolysis. We were also interested by the behaviour of tetrahydrocarbazoles in these reaction conditions. We were pleased to observe the formation of the *cis*-2,3-dihydroxyindolines **9n-s** which contain either electron-donating (**9o**), halogens (**9p,q**) or electron-withdrawing (**9r,s**) substituents. This result is in contrast with our previous direct methoxylation conditions in which α -methoxy tetrahydrocarbazoles were obtained instead of the desired 2,3-dimethoxyindolines (Scheme 1).^[8] It proves that the MgBr_2 -mediated conditions are milder than our previous ones since **9n-s** did not evolve into α -hydroxyl tetrahydrocarbazoles.

We then turned our attention towards substrates that contain a nucleophilic entity on a three carbon-side chain born by the C3-position of **10** and **11** (Scheme 4). We expected to observe a bromocyclization as in the cases of tryptophol tryptamine and tryptophan derivatives **6** which yielded **7** (Scheme 2). However, the addition of one carbon to the linker between the indole and the nucleophile led to a different outcome.

In the case of oxygenated nucleophiles, the C2-position of the oxidized indole is intramolecularly intercepted by this nucleophile, while the C3-position is attacked by water.^[20] Hydroxy-tetrahydropyranoindolines **12a-d** were thus obtained from indoles containing a primary or a tertiary alcohol. Replacing the alcohol by a carboxylic acid led to the corresponding δ -valerolactones **12e,f**. In contrast, the regioselectivity was inverted with a nitrogenated intramolecular nucleophile, since 2-hydroxy-3,3-spiroindolines **13a-c** were obtained via intramolecular attack of the sulfonamide at the C3-position of the indole.^[19,21]



Scheme 4. MgBr₂-mediated electrochemical dearomative hydroxycyclization of indole derivatives. ^{a)} Undivided cell, graphite-SK50 anode (1.4 cm x 0.8 cm x 0.2 cm submerged), platinum plated cathode (1.4 cm x 0.8 cm x 0.2 cm submerged), constant potential of 5 V between the electrodes, **10** or **11** (0.2 mmol), MgBr₂ (0.05 mmol), CH₃CN/H₂O (3 mL/2 mL), room temperature; ^{b)} isolated yields (*diastereomeric ratio of the major isomer as drawn*) are indicated.

In order to have a better understanding of these oxidative dearomatizations of N-substituted indoles, cyclic voltammetry (CV) of the reactants in acetonitrile and water were recorded (Figure 1). Similarly, to our bromocyclization of tryptophol and tryptamine derivatives **6**, N-Ts skatole **1a** is oxidized at a higher potential than MgBr₂.^[12j,22] Moreover, the CV of a mixture of N-Ts skatole **1a** and MgBr₂ shows an increase of the current intensity of the oxidation peak of MgBr₂ into presumably Br₂. It is an argument

for the selective oxidation of MgBr₂ into an electrophilic bromine intermediate.

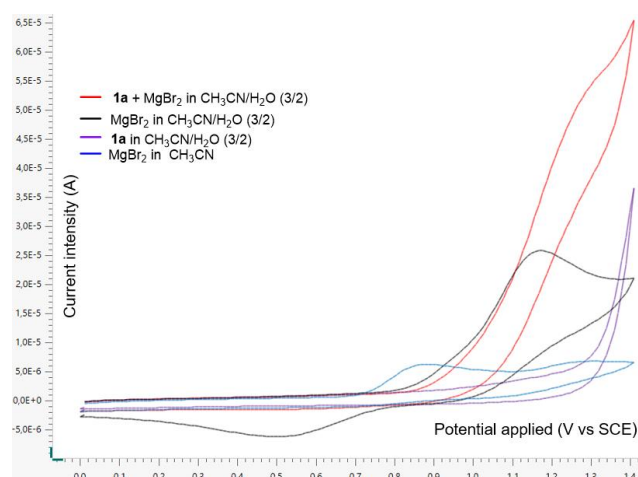
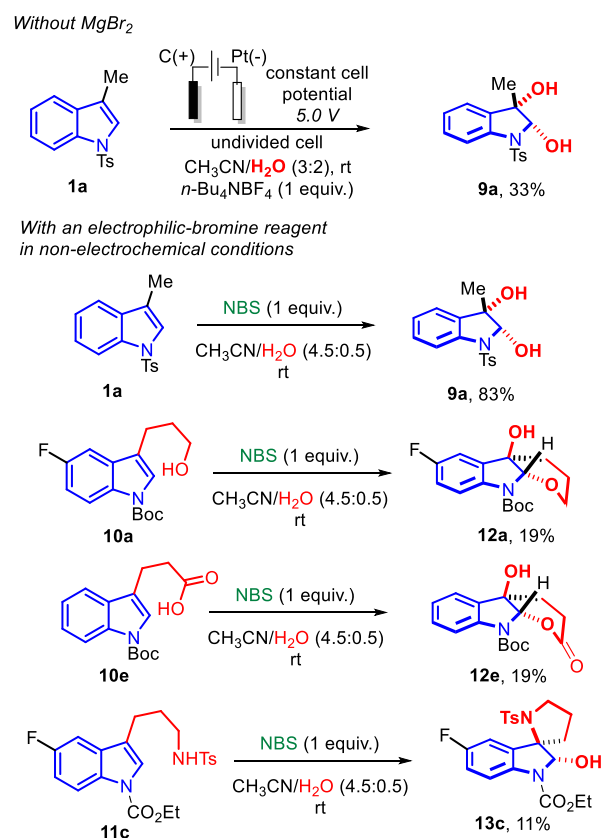


Figure 1. Cyclic voltammograms of reactants in a mixture of acetonitrile and water. A glassy carbon disc (diameter 3 mm) working electrode, a platinum wire counter electrode and a saturated calomel electrode (SCE) as reference electrode were used at a scan rate of 100 mV/s; 0.05 mmol **1a** and/or 0.025 mmol MgBr₂, 1 mmol nBu₄NBF₄ in 10 mL of CH₃CN/H₂O (3:2) or CH₃CN.

We then performed control experiments to get additional insights whether this reaction could proceed via the formation of bromonium intermediate **B** from electrogenerated Br₂ or via direct oxidation of the indole into radical cation **A** (Scheme 5).



Scheme 5. Control experiments.

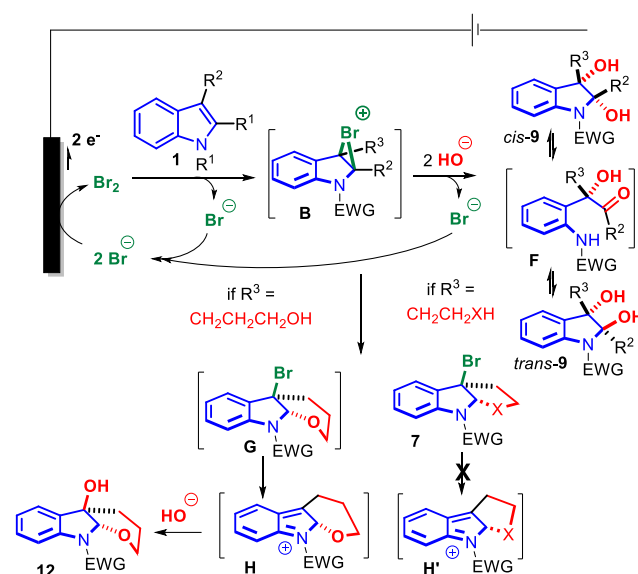
Removing MgBr_2 and using $n\text{Bu}_4\text{NBF}_4$ as electrolyte with a 5V cell potential led to a significant decrease of the yield of **9a** from 74% (Scheme 2) to 33% (Scheme 4). The reaction is sluggish and the formation of several by-products was observed. The fact that **9a** could be obtained without MgBr_2 proves that the dihydroxylation could be performed by a direct oxidation of NTs-skatole **1a** at the anode into a radical cation **A**. However, this process is significantly less efficient in comparison to the use of MgBr_2 . It may indicate that in the presence of MgBr_2 , the major pathway involves the anodic formation of an electrophilic bromine reagent such as Br_2 followed by formation of bromonium ion **B**. Avoiding the direct oxidation of **1a** at the anode seems to allow a better chemoselectivity.

To prove that an ephemeral electrophilic bromine reagent could be involved in the dihydroxylation and hydroxycyclisation reactions, the reaction of **1a**, **10a**, **10e** and **11c** with NBS as an electrophilic bromine reagent in non-electrochemical conditions led to the formation of **9a**, **12a**, **12e** and **13c** albeit in a significantly lower yield in the three last cases. It tends to confirm that in our electrochemical conditions **9a** could be generated from bromonium ion **B**.

In our recent electrochemical bromocyclization of **6** into bromofuranindolines and bromopyrroloindolines **7** which were conducted in the same conditions, it seems obvious that electrogenerated Br_2 reacts with **6** to form bromonium bridge **B** which is then intramolecularly opened to deliver **7**.^[13] It is in itself a clue that, in these reported conditions with MgBr_2 , **1a** could electrochemically be converted into **B** which could then lead to **9a** upon reaction with water.

Our mechanistic hypothesis could be summarized in Scheme 6. In all cases, we believe that the major pathway involves the two electrons anodic oxidation of two bromides into one bromine which could react with the C2=C3 bond of the indole nucleus to deliver bromonium ion **B**. The direct oxidation of indole **1** into a radical cation **A** could not be ruled out and may also co-exists as a minor pathway. Addition to **B** of hydroxide ions, which would have been formed via reduction of water at the cathode, could then lead to dihydroxyindoline **9** via intermediates **C**, **D** or **E** as depicted in Scheme 1. The *cis/trans* ratio observed for **9** is probably the result of a thermodynamic equilibrium via epimerisation at the C2-position through formation of ketone intermediate **F**, as it was previously observed.^[17d] The reason why the *cis* isomer in the case of a Ts group and the *trans* isomer in the case of an acyl group are respectively preferred are not clear to us.^[23] Intramolecular opening of **B** is also possible in presence of a nucleophilic entity in the C3-position of the indole nucleus which would deliver brominated tricyclic compounds **G** and **7**. The former could then be converted to hydroxypyranindoline **12** probably via extended iminium **H**. In the latter case,

bromofuranindolines and bromopyrroloindolines **7** are stable and could be isolated since the formation of the corresponding iminium **H'** would be less favoured due to its ring strain.



Scheme 6. Mechanistic hypothesis.

In summary, a simple electrochemical protocol to perform the dearomative dihydroxylation and hydroxycyclisation of indoles in presence of MgBr_2 without the need of an additional electrolyte has been described. We postulate that the major pathway involves the electrochemical generation of an electrophilic bromine reagent from MgBr_2 which could lead to oxidation of the indole into a bromonium ion. Upon reaction with water, this intermediate is transformed into 2,3-dihydroxyindolines. In presence of an intramolecular nucleophile and water, hydroxycyclization occurs leading to hydroxy-tetrahydropyranoindolines or 2-hydroxy-3,3-spiroindolines.

Experimental Section

Electrochemical reactions were performed with ElectraSvn 2.0 package (IKA) using the constant voltage mode. To a 10 mL vial with a stir bar were successively added the substituted indole **2** or **4** (0.2 mmol), MgBr_2 (0.05 mmol, 0.25 equiv), 2.0 mL of distilled H_2O and 3.0 mL of CH_3CN (0.04 M). The vial was covered with a screw-cap. The electrolysis was carried out at RT using a constant voltage of 5 V between a graphite anode and a platinum plate cathode (1.4 x 0.8 x 0.2 cm submerged in solution for each electrode) and a distance of 0.6 cm between the two electrodes) with stirring (500 rpm). The complete consumption of the starting indole derivative was checked by TLC (35% to 50% AcOEt /petroleum ether). The reaction was then quenched with H_2O and diluted with AcOEt . The organic and aqueous phases were separated. The aqueous phase was then extracted twice with AcOEt . The combined organic phases were then dried over MgSO_4 , filtered and concentrated under vacuum. The crude was then purified by flash column chromatography or preparative TLC (35% to

50% AcOEt/ petroleum ether). *Note:* Most of the dihydrovindolines are obtained as a mixture of *trans* and *cis* diastereoisomers. The ^{13}C NMR signals of C2 and C3 are deshielded (downfield) of approximately 5 ppm for the *trans* isomer in comparison to the *cis* isomer. The ^1H NMR signal of the proton at C2 is deshielded (downfield) of approximately 0.2 ppm for the *trans* isomer in comparison to the *cis* isomer.

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