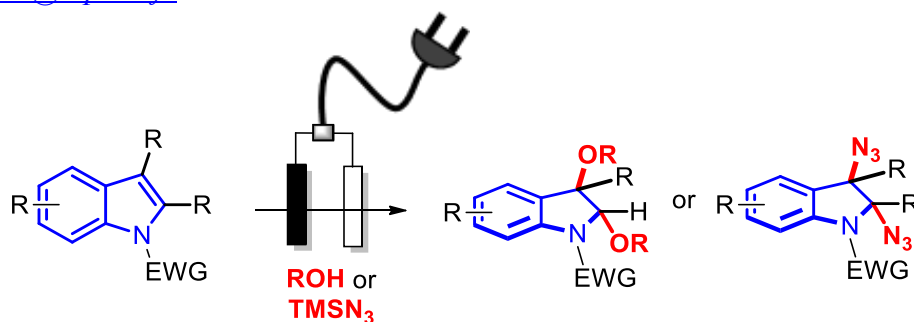


# Electrochemical dearomative 2,3-difunctionalization of indoles

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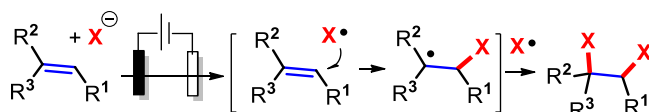
**Abstract:** We report the use of electrochemistry to perform a direct oxidative dearomatization of indoles leading to 2,3-dialkoxy or 2,3-diazido indolines under undivided conditions at a constant current. This operationally simple electro-oxidative procedure avoids the use of an external oxidant and displays an excellent functional group compatibility. The formation of the two C-O or C-N bonds is believed to arise from the oxidation of the indoles into radical cation intermediates.

The direct difunctionalization of double bonds is a field of intense synthetic efforts since it allows the formation of two new bonds via the introduction of two functional groups. Indeed, such transformation of alkenes or styrenes is very well documented and usually requires the use of an external stoichiometric oxidant.<sup>1</sup> In the last years, electrochemistry has been rediscovered to be a powerful sustainable synthetic tool in organic chemistry, thanks to the recent discovery of selective reactions and to easy-to handle apparatus or electrolysis set-ups which render electrochemistry accessible to all organic chemists.<sup>2</sup> Along with the bloom of photoredox catalysis, this rebirth of electrosynthesis has enabled the development of external oxidant-free methods for the highly efficient and selective difunctionalization of alkenes in mild conditions which usually involves the generation of a radical intermediate which adds to the alkene (Scheme 1).<sup>3</sup> Performing the direct functionalization of a double bond imbedded in an aromatic heterocycle results in a more challenging dearomatization process<sup>4</sup> and provides three-dimensional chemicals of high added value.<sup>5</sup> It is particularly interesting to perform such dearomatization reactions on the indole nucleus due to the biological importance of this heterocycle. A myriad of dearomative difunctionalizations of indoles are known,<sup>6</sup> including our own work,<sup>7</sup> which generally require the use of a strong oxidizing agent. In contrast, electrochemistry has been scarcely explored in dearomatization reactions.<sup>3a,h,8,9</sup> In this context, we would like to report the electrochemical straightforward dearomatization of indoles with the formation of two carbon-heteroatom bonds (C-O or C-N).

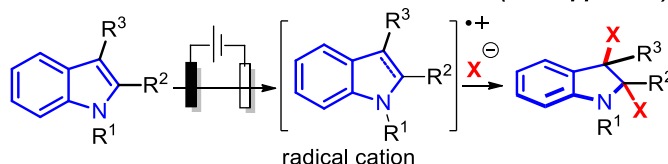
In the past 6 years, we have investigated the reactivity of N-acyl indoles in dearomatization reactions including oxidative couplings with nucleophiles.<sup>7c-f</sup> Following our synthesis of benzofuro[3,2-*b*]indolines via a (3+2) annulation between N-acyl indoles and phenols mediated by DDQ and FeCl<sub>3</sub>,<sup>7c</sup> Lei and co-workers described an electrochemical version of our reaction with improved yields and an extended scope.<sup>8a</sup> In line with our interest in dearomatization reactions of N-acyl indoles, it inspired us to explore the electrochemical oxidation of N-acyl indoles in presence of nucleophiles through, presumably, the oxidation of the indole nucleus into a radical cation which is, mechanistically, in contrast to most of the electrochemical difunctionalization of alkenes (Scheme 1).<sup>8a,c</sup>

## Scheme 1. Electrochemical difunctionalization of alkenes and heteroarenes.

### Electrochemical difunctionalization of alkenes



### Electrochemical dearomatization of indoles (this approach)

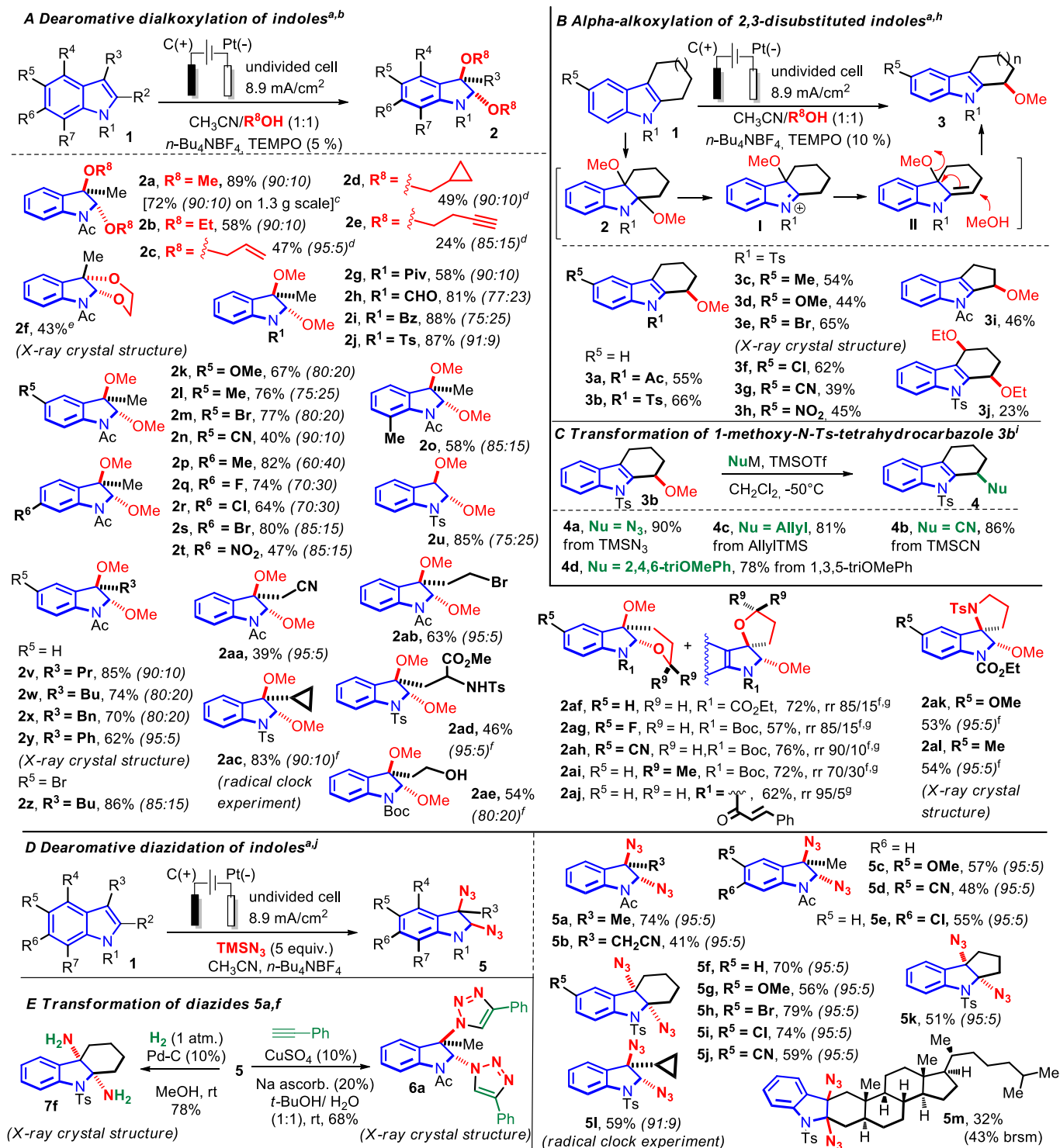


As a proof-of-principal experiment, we studied the 2,3-bismethoxylation of N-Ac skatole **1a** (Scheme 2, A).<sup>9,10</sup> The electrolysis of **1a** at a constant current of 8.9 mA/cm<sup>2</sup> with a graphite anode and a platinum cathode in a 1:1 mixture of MeOH and acetonitrile in an undivided cell and *n*-Bu<sub>4</sub>NBF<sub>4</sub> as the electrolyte at room temperature, yielded the expected 2,3-dimethoxyindoline **2a** in 77% yield as a 9:1 mixture of diastereoisomers in favor of the *trans* addition of the two methoxy groups. The use of 5 mol% of TEMPO allowed us to improve the yield to 89% and to avoid decomposition of **1a**. It was possible to implement this transformation on gram scale. The dialkoxylation could also be performed in ethanol leading to **2b** or with functionalized alcohols such as allyl alcohol, cyclopropyl methanol, homopropargyl alcohol and ethylene glycol to yield indolines **2b-2f**. The electron-withdrawing substituent on the nitrogen of the indole was next evaluated and indolines **2g-j** containing pivaloyl, formyl, benzoyl and tosyl groups were obtained. The nature of the substituents on the benzene ring was next scrutinized. The reaction tolerates electron-donating groups, halogens or electron-withdrawing groups at C5, C6 or C7 positions (**2k-t**). Indoline **2u** was obtained efficiently from 2,3-unsubstituted-N-Ts-indole. The dearomative dimethoxylation reaction proceeds well with alkyl groups or phenyl substituents at the C3 position (**2v-z**). More interestingly, the mild conditions of the reaction allow to preserve functional groups on the C3-side chain: cyano-containing indoline **2aa** and bromo-containing indoline **2ab** are obtained without, respectively, hydrolysis or nucleophilic substitution by methanol. Impressively, dimethoxylation of a 3-cyclopropylindole could be performed without noticeable opening of the cyclopropyl group leading to cyclopropylindoline **2ac**.

The dimethoxylated indolines **2ad,ae** were obtained from tryptophan or tryptophol derivatives, despite the presence of a nucleophilic entity on their C3-side chain. Adding one carbon to the C3-side chain led to intramolecular trapping by the nucleophile. In the case of alcohols, methoxy-tetrahydropyranoindolines **2af-aj** were obtained as the major products via intermolecular addition of methanol at the C3 position. In contrast, tosylamide-containing C3-side chains led selectively to valuable *trans*-spirocyclic indolines **2ak,al**, presumably via initial intramolecular trapping of the indole radical cation at C3.

The reactivity of tetrahydrocarbazoles in the same oxidative conditions was then examined (Scheme 2, B). In contrast to 3-monosubstituted N-acylindoles, alpha-monomethoxylation occurred.<sup>11</sup> This formal benzylic C-H functionalization likely proceeds via the dearomative dimethoxylation of the C2=C3 bond followed by elimination of the methoxy at C2 of **2** and isomerization of the iminium **I** into enamide intermediate **II** which could be attacked by methanol to yield **3** upon allylic nucleophilic substitution.<sup>9,11a-c</sup> Alpha-methoxy carbazoles were thus obtained with acetyl or tosyl groups on the nitrogen (**3a,b**) and electron-donating (**3c,d**), halogens (**3e,f**) or electron-withdrawing (**3g,h**) groups on the benzene part. The reaction could also be extended to cyclopentaindole **3i**. Unfortunately, 2,3-dimethyl-N-Ts-indole was not a competent substrate. Surprisingly, with ethanol, two alkoxylation occurred on the two positions vicinal to the indole ring and diethoxyindoline **3j** was obtained. Methoxy-N-Ts-tetrahydrocarbazole **3b** could be used as a platform to access molecular diversity. Addition of various nucleophiles leads to tetrahydrocarbazoles **4** substituted respectively by an azide (**4a**), a cyanide (**4b**), an allyl (**4c**) and an arene (**4d**) (Scheme 2, C).<sup>11c</sup>

## Scheme 2. Electrolysis of indoles



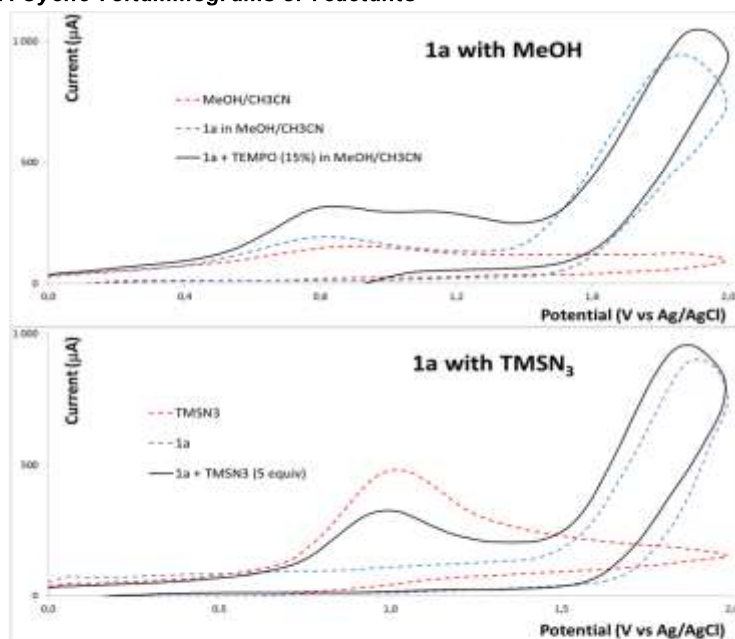
<sup>a</sup> Undivided cell, graphite-SK50 anode (1.4 cm x 0.8 cm x 0.2 cm submerged), platinum plated cathode (1.4 cm x 0.8 cm x 0.2 cm submerged), constant current of 10 mA ( $J = 8.9 \text{ mA/cm}^2$ ), 5 mL of solvent, room temperature; isolated yields (*diastereomeric ratio*) are indicated. <sup>b</sup> **1** (0.4 mmol), TEMPO (0.02 mmol), *n*-Bu<sub>4</sub>NBF<sub>4</sub> (0.4 mmol), R<sup>8</sup>OH/CH<sub>3</sub>CN (2.5 mL/2.5 mL); <sup>c</sup> anode (0.8 cm x 3.4 cm x 0.2 cm submerged), cathode (3.4 cm x 0.8 cm x 0.2 cm submerged), constant current of 15 mA ( $J = 5.5 \text{ mA/cm}^2$ ), **1** (8 mmol), TEMPO (0.0256 mmol), *n*-Bu<sub>4</sub>NBF<sub>4</sub> (2 mmol), MeOH/CH<sub>3</sub>CN (8 mL/8 mL); <sup>d</sup> in AllylOH/CH<sub>3</sub>CN (1 mL/4 mL) or cyclopropyl methanol/CH<sub>3</sub>CN (1.5 mL/3.5 mL) or homopropargyl alcohol/CH<sub>3</sub>CN (1.5 mL/3.5 mL); <sup>e</sup> in OH(CH<sub>2</sub>)OH/DMF (1.5 mL/3.5 mL); <sup>f</sup> on 0.2 mmol of **1**; <sup>g</sup> regioisomeric ratio; <sup>h</sup> **1** (0.2 mmol), TEMPO (0.03 mmol), *n*-Bu<sub>4</sub>NBF<sub>4</sub> (0.2 mmol), MeOH/CH<sub>3</sub>CN (2.5 mL/2.5 mL); <sup>i</sup> **3** (0.2 mmol), NuM (0.3 mmol), TMSOTf (0.04 mmol), CH<sub>2</sub>Cl<sub>2</sub> (2 mL), -50°C; <sup>j</sup> **1** (0.2 mmol), TMSN<sub>3</sub> (1 mmol), *n*-Bu<sub>4</sub>NBF<sub>4</sub> (0.2 mmol), CH<sub>3</sub>CN (5 mL).

Next, we evaluated the possibility of forming two C-N bonds instead of the C-O bonds during the electrochemical oxidative dearomatization of indoles by replacing methanol by a nitrogen-containing reagent.<sup>3h</sup> During recent developments in diazidation of alkenes, very few examples of diazidation of indoles were reported using an external oxidant.<sup>12</sup> Very recently, a powerful electrochemical general diazidation of alkenes with a manganese electrocatalyst was published in which only one example from a 2,3-unsubstituted indole is described.<sup>3a</sup> Eventually, the electrolysis of N-Ac skatole in presence of trimethylsilyl azide led to 2,3-diazide indoline **5a** with an excellent *trans*-diastereoselectivity (Scheme 2, D). This electrochemical diazidation reaction is compatible with a nitrile group on the C3-side chain of the indole (**5b**), electron-donating (**5c**) or electron-withdrawing (**5d**) groups or halogens (**5e**) on the benzene ring. In contrast to the electrolysis in presence of methanol, the dearomatized *cis*-products **5f-k** were also obtained from differently substituted N-Ts tetrahydrocarbazoles or cyclopentaindole. Remarkably, it allows to create diastereoselectively two contiguous tetrasubstituted stereogenic centers. As for the dimethoxylation reaction, the diazidation proceeded without noticeable opening of the cyclopropyl ring in the case of **5l**. Finally, the formation of indoline **5m**, presumably *cis*, through diazidation of a steroid-derived indole demonstrates the versatility of this electrochemical protocol towards complex substrates bearing C-H bonds prone to oxidation.<sup>13</sup> Indeed, diazide-containing indolines **5** were poised to synthetic transformations. A double click reaction could be performed on **5a** with phenylacetylene yielding *trans*-bistriazole **6** and diazide **5f** could be reduced to *cis*-2,3-diamine-containing indoline **7** (Scheme 2, E).

We next focused our attention to the mechanism of these dearomative difunctionalizations of indoles. No catalytic current was observed for TEMPO in presence of **1a** by cyclic voltammetry (see SI).<sup>2a</sup> Moreover, the dearomative dimethoxylation of **1** could be performed without TEMPO in satisfactory yields. It is therefore unlikely that TEMPO acts as a mediator to directly oxidize the N-Ac indole **1** in the dimethoxylation reaction.<sup>14</sup> The syntheses of **2ac** and **5l** represent radical clock experiments (Scheme 2, A and E). The fact that the cyclopropyl group at the C3-position did not undergo ring opening for each reactions seems to indicate that a radical is probably not formed at the C3-position of the indole. Cyclic voltammetry experiments (see SI) suggest that methanol or TMSN<sub>3</sub> are respectively involved in the reduction process at the cathode (see SI) liberating respectively methoxide or azide anions.<sup>15</sup> While NAc skatole **1a** is oxidized before methanol or TMSN<sub>3</sub> (see SI), oxidative waves of methoxide or azide anions are observed at lower potentials than the oxidative wave of **1a** (Scheme 3, A and SI). To verify if methoxy or azide radicals are responsible for the dimethoxylation or diazidation, these reactions were each conducted at a constant potential of 1.3V (vs Ag/AgCl), between the oxidative waves of the methoxide or azide anions and the oxidative wave of **1a** (Scheme 3, B). No reaction was observed in the dimethoxylation reaction, while a low yield of diazide **5a** (23%) was obtained along with recovered **1a** and unidentified byproducts. Moreover, replacing TMSN<sub>3</sub> by NaN<sub>3</sub> or Bu<sub>4</sub>NN<sub>3</sub>, which are well known to generate the azide radicals by anodic oxidation, resulted in no reaction. Interestingly, in presence of an excess of TEMPO, both the dialkoxylation and the diazidation did not proceed and only the starting N-Ac indole was recovered which is in sharp contrast to the azidooxygenation of alkenes developed recently by Lin which involved azide radicals.<sup>3a,d,16</sup> More importantly, we noticed that in our classical constant current conditions, the potential of the anode was above 2V (vs Ag/AgCl) for each reactions, which is superior to the oxidation potential of **1a**.<sup>17</sup> We therefore believe that N-substituted indole **1** is oxidized directly at the anode into radical cation intermediate **III**. Methoxide or azide anions produced at the cathode could then react at the C3-position of **III** accompanied by an oxidation process at the anode (Scheme 3, C). This process could be simultaneous or stepwise via initial addition of the nucleophile to **III** leading to a radical intermediate at C2 which could then be oxidized.<sup>18</sup> The resulting iminium ion **IV** is poised to be trapped by a second molecule of methoxide or azide to eventually deliver **2** or **5** as their more stable isomers. In the case of 3-substituted indoles, the methoxy or azides are *trans* to each other to avoid electronic repulsion, while 5,6 or 5,5-fused ring systems greatly favor the *cis* isomer.

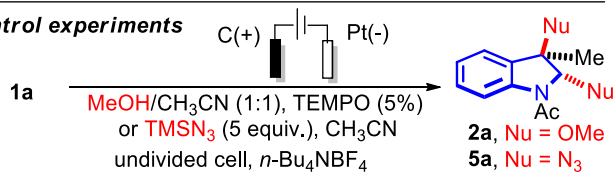
### Scheme 3. Mechanistic considerations.

#### A Cyclic voltammograms of reactants



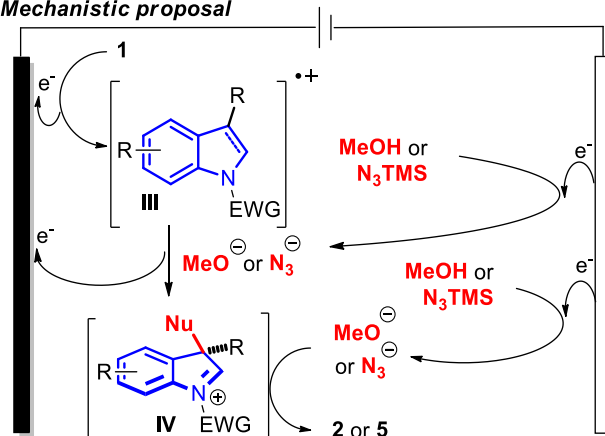
Recorded from -2V to 0V to -2V; only the [0, +2V] range is shown. Glassy carbon working electrode; Pt counter electrode, Ag/AgCl (3M aq. KCl) ref electrode; 500mV/s; 0.012M **1a**; 0.0017M TEMPO; 0.6M TMSN<sub>3</sub>; 0.1 M n-Bu<sub>4</sub>NBF<sub>4</sub> in 5mL MeOH/CH<sub>3</sub>CN (1:1, top CV) or CH<sub>3</sub>CN (bottom CV).

#### B Control experiments



Nucleophile	Electrolysis conditions	Results
MeOH	constant potential 1.3 V (vs Ag/AgCl)	No reaction
TMSN <sub>3</sub>	constant potential 1.3 V (vs Ag/AgCl)	<b>5a</b> (23%) + by-products + recovered <b>1a</b>
Bu <sub>4</sub> NN <sub>3</sub> or NaN <sub>3</sub>	constant current (8.9 mA/cm <sup>2</sup> )	No reactions
MeOH or TMSN <sub>3</sub>	constant current (8.9 mA/cm <sup>2</sup> ) TEMPO (1.5 equiv.)	No reactions
MeOH or TMSN <sub>3</sub>	"Classical Conditions" constant current (8.9 mA/cm <sup>2</sup> ) Observed potential >2V (vs Ag/AgCl)	<b>2a</b> (89%) or <b>5a</b> (74%)

#### C Mechanistic proposal



The present diazidation reaction is in contrast with the electrochemical diazidation of alkenes developed by Lin, in which oxidation of  $\text{NaN}_3$  delivers catalytically an azide-manganese radical which adds to the alkene followed by trapping of the subsequent carbon radical by a second azide-manganese radical species.<sup>3a</sup>

In conclusion, we deployed electrochemistry to perform a general oxidative and dearomative difunctionalization of indoles with the formation of two C-O or two C-N bonds. This reaction likely proceeds via anodic oxidation of the N-substituted indole into a radical cation which could be trapped by alcohols or azide yielding three-dimensional 2,3-dialkoxyindolines or 2,3-diazidoindolines with a broad scope. These undivided electrolytic conditions avoid the use of an external oxidant and should inspire the development of other dearomatization reactions to access high added-value architectures from flat and readily available starting materials.

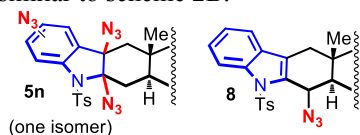
*We gratefully acknowledge Dr. Laurence Grimaud (ENS Paris) and Dr. Maxime Vitale (Chimie Paris Tech) for helpful discussions. JW and YD thank the China Scholarship Council (CSC) for their respective PhD fellowships. We also gratefully acknowledge the ANR (ANR-17-CE07-0050; "ArDCo"), the Université Paris Sud and the CNRS for financial support.*

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- (13) Isolated with 4% of dearomatized triazide **5n** and 4% of alpha azidation product **8**. The former arises from azidation of one of the C-H bond (C5 or C6) of the indole nucleus of **5m**, while the latter may arise from **5m** through an elimination similar to scheme 2B.



- (14) It is unclear to us how the addition of a small amount of TEMPO slightly increase the yield and avoid decomposition of **1**. It might prevent the increase of the potential at the anode and therefore the decomposition of **1** at the end of the reaction when the concentration of **1** is too low.
- (15) In the dimethoxylation reaction, gas evolution is observed at the cathode, which we believe is hydrogen produced by the reduction of methanol. In the diazidation reaction, the reduction process at the cathode is unclear to us. Hexamethyldisilane was not detected by NMR when we performed the reaction in deuterated acetonitrile. It is conceivable that adventitious water in the medium could react with TMSN<sub>3</sub> and led to formation of protons which are reduced at the cathode as suggested by the observation of gas evolution at the cathode.
- (16) If a N<sub>3</sub> radical was adding first to the indole, we would have expected the trapping of the resulting carbon radical with TEMPO (see ref 3a,d) which is not the case (Scheme 3, B). It is likely that TEMPO is oxidized instead of **1a** and the resulting excess oxoammonium ion could react with methanol or TMSN<sub>3</sub>.
- (17) Indeed, the potential at the anode is quite high and could lead to side reactions. However, we have shown a reasonable functional groups compatibility during the present study.
- (18) The electrolysis of 2-cyclopropyl-N-Ts-indole with MeOH led to an intricate mixture of compounds with small amounts of indole **9** (5%) which results from the opening of the cyclopropyl by methanol. This result may suggest the existence of a radical intermediate at C2 and a step-wise process for the formation of **IV** from **III**.

