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VIP **Dearomatization** *Very Important Paper*

Unbiased C3-Electrophilic Indoles: Triflic Acid Mediated C3-Regioselective Hydroarylation of N–H Indoles**

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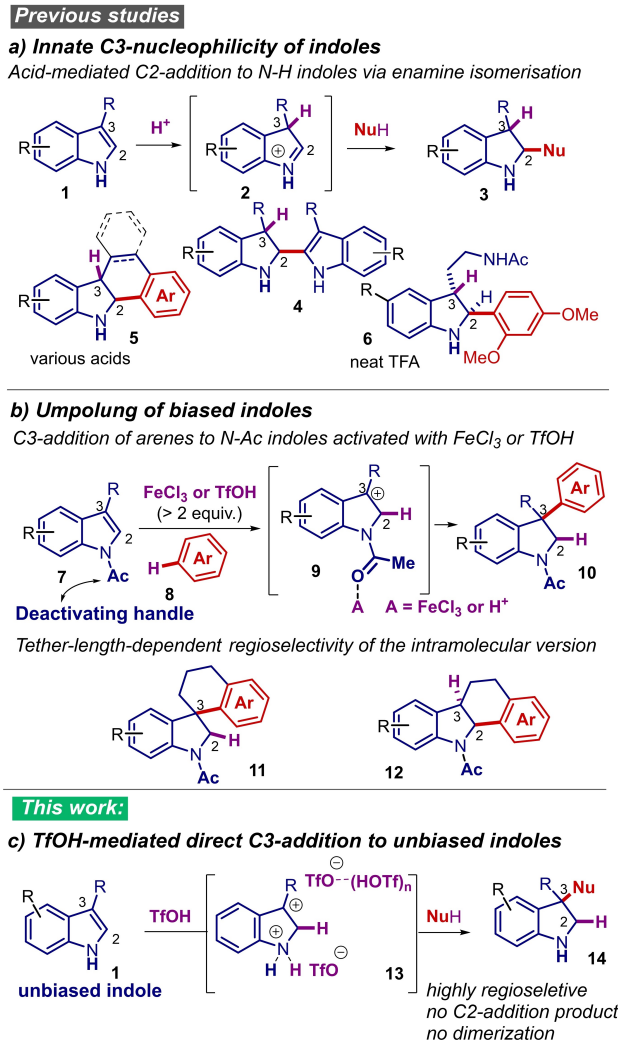
Abstract: The direct dearomative addition of arenes to the C3 position of unprotected indoles is reported under operationally simple conditions, using triflic acid at room temperature. The present regioselective hydroarylation is a straightforward manner to generate an electrophilic indole at the C3 position from unbiased indoles in sharp contrast to previous strategies. This atom-economical method delivers biologically relevant 3-arylindolines and 3,3-spiroindolines in high yields and regioselectivities from both intra- and intermolecular processes. DFT computations suggest the stabilization of cationic or dicationic intermediates with H-bonded $(TfOH)_n$ clusters.

Introduction

The indole nucleus displays a strong nucleophilicity at the C3 position,[1] allowing reactions with a range of electrophiles. In this context, addition of nucleophiles at the C2 position of N–H indoles **1** is possible under acidic conditions after protonation of the C3-position, leading to products **3** via the iminium species **2** (Scheme 1a).[2] This typical reactivity pattern has been widely exploited in dearomatization strategies.[3] However, in presence of an acid, dimerization of N–H indoles **1** into dimers **4** is often observed after C2-addition of one indole to the iminium intermediate **2**.[2a,c] The formation of compounds **5**, featuring a six-membered ring, has also been reported by intramolecular addition of arene nucleophiles (such as indoles,[2b–d] anilines[2e] or pyrroles[2f,g]) to the C2 iminium intermediate. The intermolecular addition of a nucleophile[2h,i,k,m] has been more rarely



Scheme 1. Hydroarylation of electrophilic indoles.

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achieved since it requires a more reactive species than the indole itself to prevent dimerization into **4**.[2a] For instance, the addition of 1,3-dimethoxybenzene at the C2 position of tryptamine derivatives into **6** was described by Laronze in trifluoroacetic acid.[2h] However, the regioselective addition of nucleophiles to the C3 position of **1** appears to be mechanistically less favorable since it involves the reversal of the inherent reactivity of the indole ring. Biased strategies have been developed to achieve the umpolung of indole such as the oxidation of indoles or the introduction of strong electron-withdrawing groups.[4]

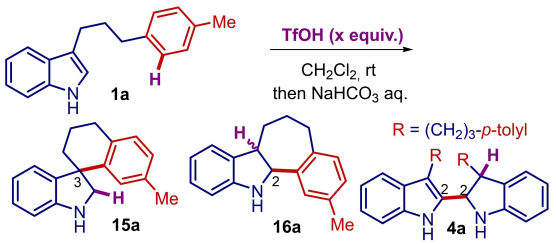
In this context and over the past decade, we aimed at developing synthetic dearomatization methods that overturn the innate reactivity of the indole nucleus using biased strategies.[5] Based on preliminary findings from the group of Nakatsuka,[6] we reported the intermolecular regioselective C3 hydroarylation of 3-substituted *N*-Ac indole derivatives **7** by electron-rich arenes **8** in presence of typically more than 2 equivalents of $FeCl_3$, or TfOH (Scheme 1b).[7–12] However, the regioselectivity of the intramolecular version of this reaction depends on the length of the tether between the indole and the arene nucleophile: a three carbon linker leads to 3,3-spirocyclic indolines **11** via the formation of a 6-membered ring,[8,12] while a two carbon linker favors the formation of six-membered ring-fused indolines **12** by addition of the arene at the C2 position.[11b] Nevertheless, this expedient access to biologically relevant spiroindolines[13] contrasts with the classical dearomatizing methods[3] relying on the typical indole nucleophilicity, including our own recent efforts using Au^I catalysis.[14] Beyond these regioselectivity issues, the reaction requires the substitution of the indolic nitrogen by an acetyl group, which has to be incorporated upstream and which removal usually necessitates rather strong conditions (aq. HCl, EtOH, 85 °C).

Aiming to develop a truly unbiased method for the generation of C3-electrophilic indoles, we finally would like to report that non-deactivated indoles **1** could be subjected to the addition of nucleophiles at C3 in presence of TfOH (Scheme 1c). Herein, we describe the development of a rare redox-neutral C3 regioselective dearomative arylation[9] of NH-indoles **1** for the synthesis of 3-arylindolines and 3,3-spiroindolines and provide a mechanistic rationale supported by DFT calculations which involve cationic or dicationic intermediate **13** stabilized by H-bonded triflic acid clusters.

Results and Discussion

We started our study by optimizing the dearomative cyclization of N–H indole **1a**, which contains a nucleophilic *para*-tolyl moiety (Table 1). Under strong acidic conditions and without an acetyl deactivating group, we envisioned that this reaction might lead to the desired spiroindoline **15a**, but we were most likely expecting the formation of the seven-membered ring compound **16a** and the dimer product **4a**.[2a–g] Indeed, treating **1a** with 1.0, 1.5 or 2.0 equivalents of TfOH mainly led to dimer **4a** (entries 1–3). Strikingly, increasing the amount of TfOH to 2.5 equivalents led exclusively to the formation of the 3,3-spiroindoline **15a** without any traces of **16a** or **4a** (entry 4).

Table 1: Optimization of the intramolecular hydroarylation of **1a**.[a]

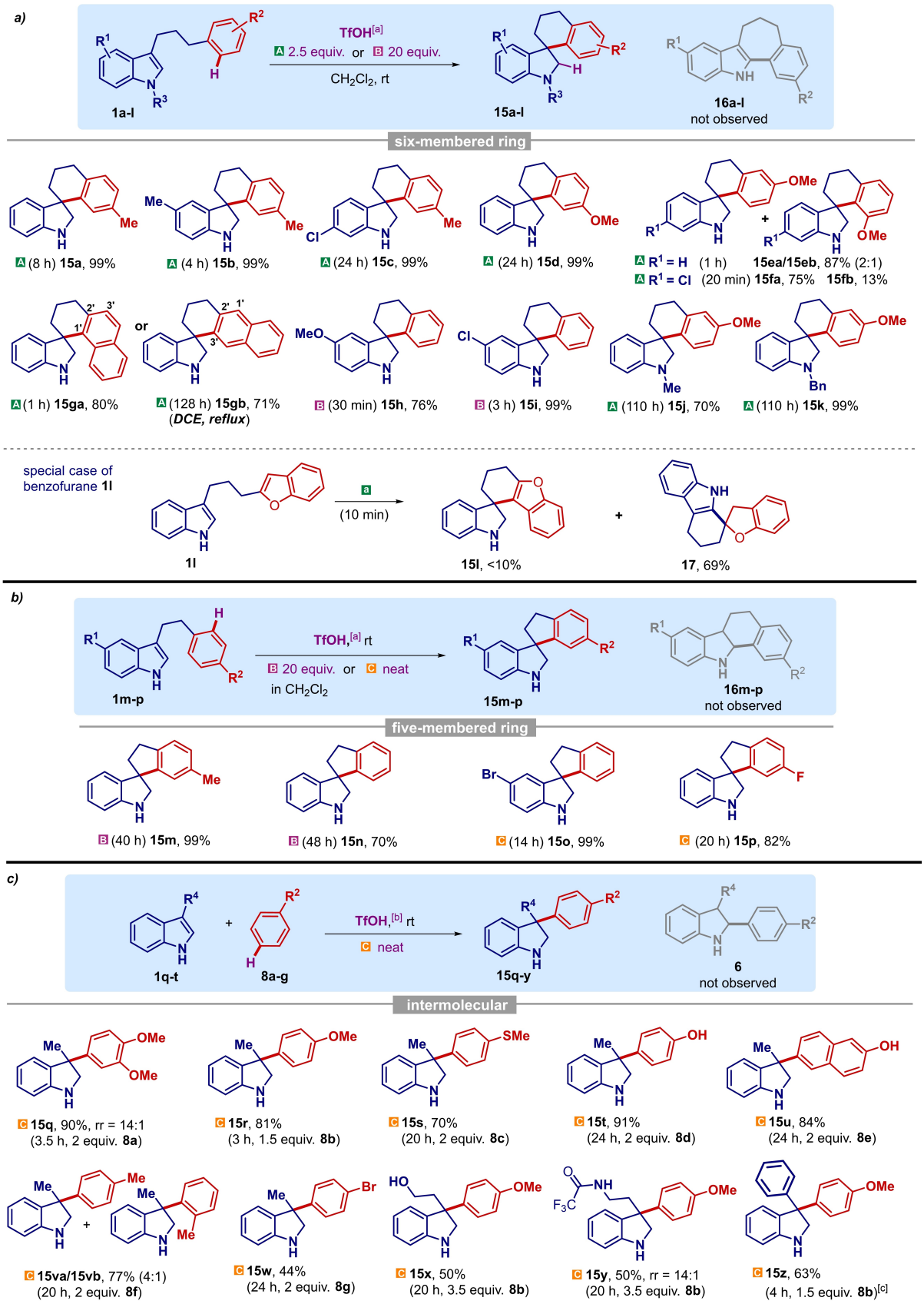


Entry[a]	Equiv. TfOH	NMR yield [%][b]		
		15a	**16a**	**4a**
1	1	0	0	80
2	1.5	2	0	54
3	2.0	4	0	62
4	2.5	99	0	0

[a] Reactions conditions: 0.05 mmol of **1a** and x equiv. of TfOH in 0.5 mL of CH_2Cl_2 at rt for 20 h followed by work-up with saturated aqueous $NaHCO_3$. [b] Determined by ^{1}H-NMR using CH_2Br_2 as internal standard.

This finding led us to the conclusion that the *N*-Ac deactivating group is not mandatory to orientate the hydroarylation towards the C3 position. *This discovery represents a major practical and conceptual advance*: in addition to avoid the undesirable introduction and removal of a functional group, it also demonstrates that the delocalization of the nitrogen lone pair into an electron-withdrawing group is not essential to generate the C3 electrophilicity of the indole nucleus.

We next explored of the scope of this reaction to demonstrate its utility (Scheme 2a). While compound **15a** could be isolated in 99 % yield with 2.5 equivalents of TfOH, electron-richer and -poorer indoles also proved to be reactive, leading to 5-methyl and 6-chloro spiroindolines **15b** and **15c** in 99 % yield. The nature of the nucleophilic arene was then studied. Switching from a *para*-tolyl to a *para*-anisyl group led uneventfully to **15d** in 99 % yield. Moving the methoxy group of the anisole to the *meta* position allowed to greatly increase the rate of the hydroarylation, leading to the fast formation of both *para* and *ortho* regioisomers **15ea**/**15eb** (87 %) in a 2:1 ratio and **15fa** (75 %) as well as **15fb** (13 %) in a 5:1 ratio. A 2′-naphthyl group could also be employed as the internal nucleophile via its 1′-position, leading in 1 h to spiroindoline **15ga** (80 %). Interestingly, performing this reaction in refluxing dichloroethane for a prolonged time (128 h) delivered regioisomer **15gb** (71 %) via the reaction of the 3′-position of the naphthyl group. It seems obvious that a retro Friedel–Crafts/Friedel–Crafts process from the kinetic product **15ga** to the thermodynamic one **15gb** is involved in this second set of reaction conditions. Using a less electron-rich phenyl nucleophile required a much higher (20 equivalents) loading



Scheme 2. Scope of the TfOH-mediated C3-regioselective hydroarylation of indoles. Reactions conditions: [a] 0.1 mmol of **1a–p** and 2.5 equivalents of TfOH (A) or 20 equivalents of TfOH (B) in 1 mL of CH_2Cl_2 or in 0.5 mL of TfOH (C) at rt followed by work-up with saturated aqueous $NaHCO_3$; [b] 0.25 mmol of **1q–s** with 2–3.5 equivalents of **8** in 0.5 mL of TfOH (C) at rt followed by work-up with saturated aqueous $NaHCO_3$; [c] 0.1 mmol of **1t** with 1.5 equivalent of **8b** in 0.2 ml of TfOH (rr = regioisomeric ratio, rr > 14:1 unless otherwise noted).

of triflic acid as promotor to deliver 5-methoxyspiroindoline **15h** (76%) and 5-chlorospiroindoline **15i** (99%).

We then looked at the substitution of the indolic nitrogen and we were pleased to observed that both *N*-methyl and *N*-benzyl indoles were prone to deliver the respective spiroindolines **15j** (70%) and **15k** (99%), albeit in a significantly longer reaction time compared to the corresponding N–H indoles. Of note, we only observed the *para*-regioisomers from the internal *meta*-methoxy phenyl nucleophile.

Aiming to investigate the 2′-benzofuryl group as an internal heteroaryl nucleophile, the expected spiroindoline **15l** was produced in a poor yield, while 2′,2′-spirobenzofurane **17** was obtained as the major compound (69%). In this case, the benzofuran was probably more easily protonated than the indole ring, generating an electrophilic benzofuran cation onto which the indole moiety could add as a nucleophile.

We were also eager to study the reactivity of two-carbon-tethered substrates **1m–p** having in mind that: 1) the formation of the 5-membered ring 3,3-spiroindolines **15m–p** should be more difficult and 2) that the corresponding six-membered ring tetracyclic compounds **16m–p** should be more likely formed. In order to observe any intramolecular hydroarylation of *para*-tolyl-containing **1m**, up to 20 equivalents of triflic acid had to be employed (Scheme 2b). Gratifyingly, the C3 cyclization product **15m** (99%) was exclusively obtained instead of the expected C2 cyclization product **16m**. This result is in sharp contrast with previous results on related substrates (Scheme 1a, compounds **5**)[2b–g] including our own results with the corresponding *N*-Ac indoles (Scheme 1b; compounds **12**).[11b] A phenyl nucleophile was also competent to deliver spiroindoline **15n** (70%). Even more remarkably, upon running the reaction in pure TfOH, the less electron-rich 5-bromo indole and *para*-fluorophenyl nucleophile delivered respectively spiroindolines **15o** (99%) and **15p** (82%).

Intrigued by the regioselectivity observed for these two-carbon-tethered substrates, we wondered what would be the outcome of an intermolecular reaction in terms of reactivity and regioselectivity. As already mentioned and confirmed here, N–H-indoles have a high propensity to dimerize under acidic conditions[2a] and the previously reported addition of external nucleophiles occurred at the C2 position (Scheme 1a; compound **6**).[2h] Indeed, dimerization of 3-methylindole is mainly observed with a stoichiometric amount of TfOH in CH_2Cl_2 (Supporting Information, Table S1). However, running the reaction in pure TfOH allowed us to observe, after 3.5 h, the intermolecular hydroarylation of 3-methylindole with the addition of veratrole at the C3-position, leading to **15q** in 90% yield (Scheme 2c).[15] Once again, this C3-regioselectivity is in sharp contrast with what has been observed previously (Scheme 1a). Anisole, thioanisole, phenol, 2-naphtol and toluene were also competent nucleophiles under those conditions, leading respectively to 3-arylindolines **15r–v**. Bromobenzene was also sufficiently reactive to add to 3-methylindole, delivering **15w**. Other 3-substituted indoles such as tryptophol and *N*-trifluoroacetyltryptamine were also prone to react with anisole to yield **15x** and **15y**. No intramolecular trapping of a carbocation by the internal nucleophile could be observed in these cases. The reaction of 3-phenylindole leading to 3,3-diarylindoline **15z** was rather fast considering its steric hindrance and may be explained by the stabilization of the C3 carbocation with an aryl substituent. Unfortunately, 2,3-dimethylindole did not react with anisole (not shown).

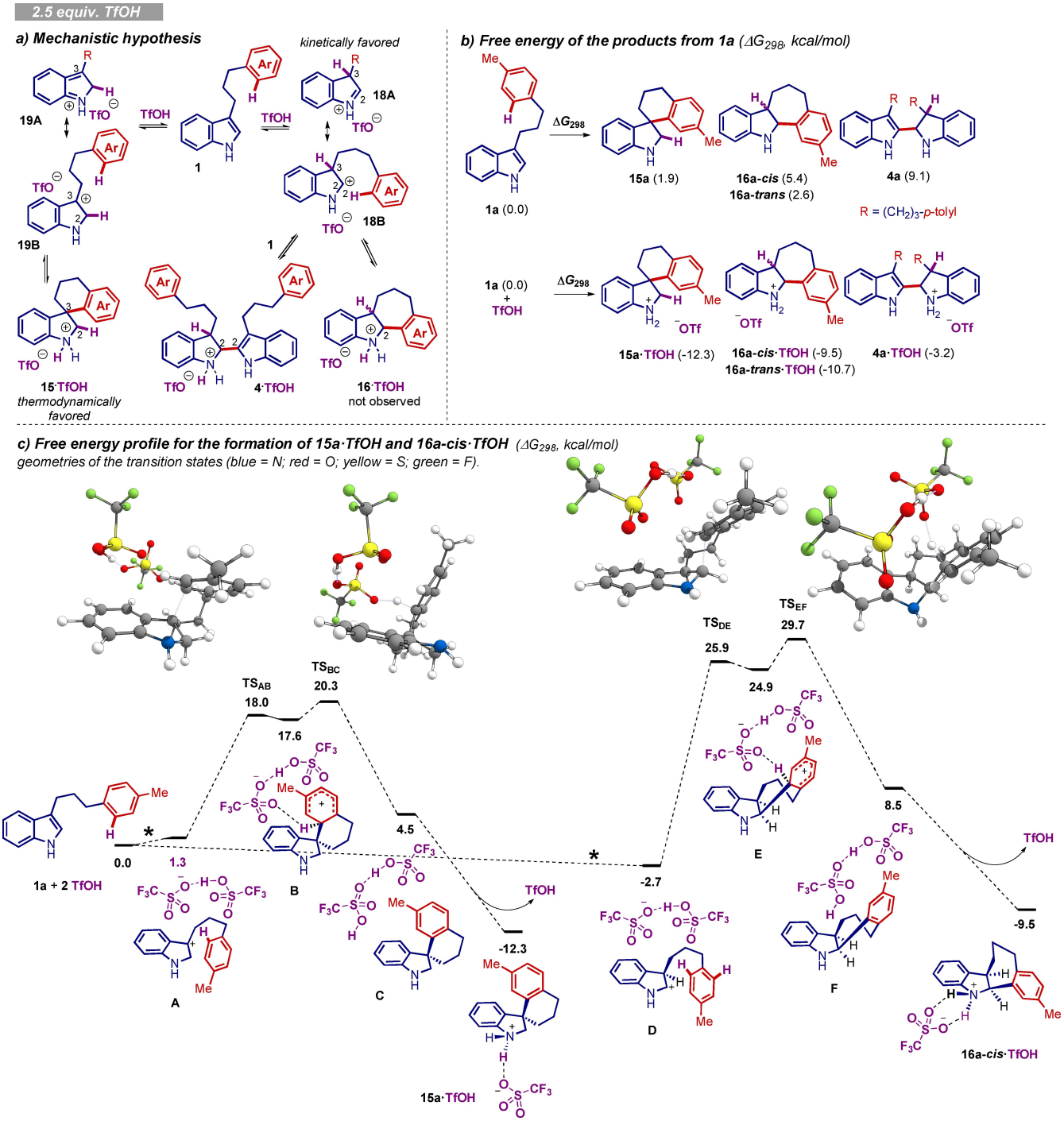
From a mechanistic point of view, it seems evident that protonation at C2 occurs, generating a carbocation at C3 onto which the electron-rich arene adds to deliver the 3-arylindolines **15**. These atypical C2-protonations of indoles have been known for decades using strong acids[16] and demonstrated by isotopic exchanges,[17] in particular when the indole ring is substituted at C3. It is also known that 3-substituted indoles undergo electrophilic substitutions at C2.[18] Finally, recent studies from our group revealed the coordination of Au^I complexes at the C2-position is possible.[19] Overall, reactions triggered by direct C2 nucleophilicity of indoles are often overlooked.[20]

To explain the exquisite regioselectivity of the reaction towards 3-arylindolines **15** without observing intramolecular additions of the arene group to the C2 position, we first elaborated the following mechanistic hypothesis for the formation of the six-membered 3,3-spiroindolines **15a–k** in presence of 2.5 equivalents of TfOH (Scheme 3a). Protonation at the C3 position of the enamine moiety of N–H indole **1** into iminium **18A** and its mesomeric C2 carbocation **18B** would likely be kinetically favored over C2 protonation into **19A/B**. Intermolecular Friedel–Crafts reaction of **18B** with another molecule of indole **1** would lead to dimer **4·TfOH** as a triflic acid salt. However, an excess of triflic acid could promote a retro Friedel–Crafts reaction of **4·TfOH**, regenerating **1** via **18**.[21] Reversible protonation of **1** could also generate extended iminium **19A** with C3 carbocation **19B** as its resonance form, which could be intramolecularly trapped into 3,3-spiroindoline triflic acid salt **15·TfOH**, which is the postulated thermodynamically favored product.

To gain more insights, we performed a DFT study, which is fully described in the Supporting Information. Geometries were optimized at the M06-2X level of theory. All atoms were described by the 6-311+G(d,p) basis set. The values discussed are Gibbs free energies (ΔG_{298}, kcal mol^{-1}) including PCM solvation correction. The three-carbon-tethered arylindoles **1a** and the two-carbon tethered arylindoles **1n** were used as model substrates. Starting with **1a**, we computed the relative stability of the possible products **15a**, **16a** and **4a** (Scheme 3b). Interestingly, we found that none of these compounds are more stable than the starting material. In particular, the experimentally isolated spiro product **15a** is less stable than **1a** by 1.9 kcal mol^{-1}, a result that was confirmed using various levels of theory. Even the dimer **4a** was found less stable than two monomers. Since the reaction is performed in the presence of an excess of TfOH, we then computed the free energy of the corresponding triflate salts. This time, the reaction of **1a** with TfOH, giving either the spiro compound **15a·TfOH**, the *cis* or *trans* seven-membered ring products **16a·TfOH**, or the dimer **4a·TfOH**, is exergonic. Therefore, the success of the reaction is likely due to the acidity of the medium and the

isolation of the spiro compounds should be the fruit of the neutralization of the triflate salts by the work-up with saturated aqueous $NaHCO_3$.

We then studied the reaction pathways. By using one explicit TfOH molecule in the computations (not shown, see the Supporting Information Figures S1–S3 for details), we found that the kinetically favored pathway is the formation of the dimer **4a·TfOH**, but it is easily reversible (Supporting Information, Figure S3). The spiro derivative **15a·TfOH** is favored thermodynamically over all species (Scheme 3b), but also kinetically over the seven-membered ring products (Supporting Information, Figures S1–S2, TS of 26.0 and 28.0 kcal mol^{-1} for respectively **15a·TfOH** and **16a-*cis*·TfOH**). While in line with the experimental results for **1a**, at



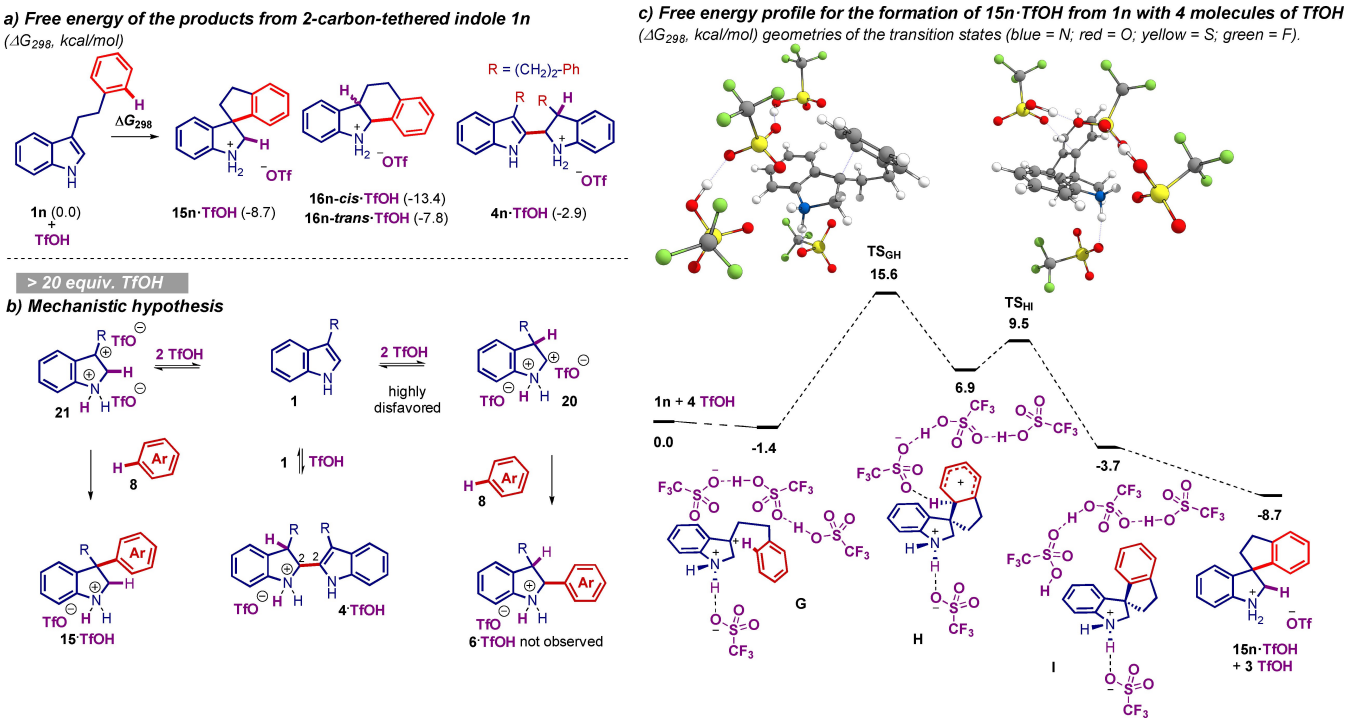
Scheme 3. Mechanistic hypothesis and free energy profile for the formation for the C3 intramolecular hydroarylation leading to six-membered spiroindolines **15a–l** using 2 equivalents of TfOH (*the free energies of the transition states for the C2- and C3-protonation are respectively 11.1 and 7.2 kcal mol^{-1} and are described in the Supporting Information, Figure S4).

least two equivalents of triflic acid are necessary to observe the formation of indoline **15a** experimentally (Table 1), which led us to introduce more explicit TfOH molecules in analogy with the recently demonstrated stabilizing effect of hydrogen bond acid-HFIP clusters.[15,22] The H-bonded $(TfOH)_2$ dimer[23] was used to model reactions promoted by 2.5 equivalents of TfOH and the cyclization barrier was significantly lowered compared to the use of only one molecule of TfOH. The computed formation of **15a·TfOH** is shown in Scheme 3c (left part). Protonation at C2 to give **A** is endergonic by 1.3 kcal mol^{-1} (with a transition state at 11.7 kcal mol^{-1}, see Supporting Information, Figure S4 for details). Nucleophilic attack of the *p*-tolyl group to the carbocationic center takes place through $\mathbf{TS_{AB}}$, lying at 18.0 kcal mol^{-1} on the free energy surface. It leads to the Wheland-type intermediate **B** at 17.6 kcal mol^{-1}. Deprotonation is the rate-determining step, $\mathbf{TS_{BC}}$ being found at 20.3 kcal mol^{-1}. As discussed above, the corresponding spiro derivative **C** is less stable than the reactants (by 4.5 kcal mol^{-1} in the presence of the $(TfOH)_2$ dimer). However, moving one TfOH to the indoline nitrogen atom places **15a·TfOH** at −12.3 kcal mol^{-1}. In contrast with the C2 protonation, the protonation at C3 is exergonic (Scheme 3c, right part: **D**, −2.7 kcal mol^{-1} with a transition state at 7.2 kcal mol^{-1}, see Supporting Information, Figure S4 for details). However, the SE_{Ar} process involves transition states that are clearly higher in energy than the previously computed ones ($\mathbf{TS_{DE}}$ 25.9 kcal mol^{-1}; $\mathbf{TS_{EF}}$ 29.7 kcal mol^{-1}). The C3 and C2 protonations can be considered reversible since the corresponding transition states are not rate determining and the activation energy difference between 6-membered ring and 7-membered ring pathways may clearly demonstrate the observed selectivity. Overall, despite a protonation equilibrium probably shifted toward the C3 side, the minor C2 protonated species **A** may be the main productive species in excess of TfOH.

In contrast, DFT computations of the cyclization of two-carbon-tether indole **1n** indicated that the related pathway via the sole protonation of the C2=C3 bond favored the cyclization at C2 into six-membered ring fused indoline **16n·TfOH** over cyclization at C3 into five-membered spiroindoline **15n·TfOH** even with two explicit TfOH molecules (Supporting Information, Figures S5, S6). Moreover, unlike the previous series, the spiro derivative **15n·TfOH** is not the most stable isomer. This time, the unobserved **16n-*cis*·TfOH** is clearly the thermodynamic product (Scheme 4a).

Importantly, the cyclization into the 5-membered-ring 3,3-spiroindolines **15m–p** and the intermolecular reaction leading to indolines **15q–z** requires experimentally a very large excess of TfOH (20 equivalents or more).

To account for the formation of **15n–z** in the presence of a large excess of acid, an alternative mode of activation of the indole with TfOH was therefore investigated. In these superacidic conditions, superelectrophilic species could be generated.[23,24] Double protonation of the indole might occur at both the nitrogen position and at C2 or C3, leading respectively to diprotonated species **20** and **21** (Scheme 4b). We reasoned that if the excess of TfOH encourages the protonation of the indole nitrogen atom, this would disfavor the protonation at C3 (1,2-dication **20**) to avoid two contiguous positive charges. By switching off



Scheme 4. Mechanistic hypothesis for the regioselective inter- and intramolecular C3 hydroarylation leading to indolines **15q–l** and five-membered-ring spiroindolines **15m–p** and free energy profile for the formation for **15n** from **1n**.

this pathway, only the 3-arylated indolines **15·TfOH** would be obtained after C2 protonation (1,3-dication **21**) and addition of arene **8**.

This hypothesis involving a dicationic intermediate was investigated by DFT computations for the cyclization of **1n** into **15n**. Interestingly, it was not possible to compute the formation of a six-membered ring product from a 1,2-dication that would arise from the protonation at C3, giving credit to the working hypothesis. In such case, TfOH was ejected from the protonated indole nitrogen atom during optimization. On the other hand, keeping one TfOH bonded to the indole nitrogen atom, it was possible to optimize the 1,3-dication and its pathway towards **15n** with an activation barrier of 35.8 kcal mol^{-1} (Supporting Information, Figure S7).[25] While the 1,3-dication hypothesis is in line with the spiro selectivity, it does not by itself explain how the reaction could take place at room temperature. We reasoned that a strongly polar environment could stabilize the 1,3-dication.[22,15] Therefore, more explicit TfOH molecules were added and once again the computed cyclization barrier was dramatically lowered (Scheme 4c).[23] By adding two TfOH to the upper triflate via hydrogen bonds, a strong stabilization of dication **G** was observed. Remarkably, this species was found more stable than the reactants (−1.4 kcal mol^{-1}), which can be attributed to the strongly polar environment provided by the $(TfOH)_3$ cluster. The free energy of the cyclization transition state $\mathbf{TS_{GH}}$ is only 15.6 kcal mol^{-1}. The corresponding Wheland intermediate also enjoys a strong stabilization (**H**; 6.9 kcal mol^{-1}) and the deprotonation transition state could be found only 2.6 kcal mol^{-1} above it ($\mathbf{TS_{HI}}$; 9.5 kcal mol^{-1}). Of course, the exact nature of the $(TfOH)_x$ clusters in the biphasic $TfOH/CH_2Cl_2$ mixture (or neat TfOH) is not known, but there is a clear trend in the computations supporting the idea of the formation of a 1,3-dication stabilized by such supramolecular assemblies (Supporting Information, Figure S7).

To summarize, the above computations show that the reaction is viable because the experimental conditions lead to ammonium triflates, hence the requirement of an excess of TfOH. The corresponding neutral products are actually less stable than the reactants. The formation of dimer **4·TfOH** of the starting indole is the kinetically favored process via protonation at the C3 position of the enamine moiety of N–H indole **1** into iminium **18**, yet it is easily reversible. It is therefore not surprising to observe such dimers, but they can be disassembled in favor of the more stable 3-arylindolines **15·TfOH**. The observed C3 over C2 arylation seems inconsistent with the preferential C3 protonation of the indole. However, even if C2 protonation is an endergonic process, arylation at C3 can be funneled nonetheless for several reasons that can be deduced from the computations:

i) Intramolecular arylations of three-carbon-tethered arylindoles **1a–k** with 2.5 equiv of TfOH: The formation of a six-membered ring is entropically favored over a seven-membered ring one. Thus, the six-membered ring pathway leading to a spiro derivative **15a–k** prevails and compensates the endergonic C2-protonation. Moreover, the use of 2.5 equiv of TfOH allows the formation of a H-bonded $(TfOH)_2$ dimer which greatly stabilizes the cationic intermediates and transition states.
ii) Intramolecular arylations of two-carbon-tethered arylindoles **1m–p** and intermolecular arylation of **1q–s** with $\geq$20 equiv of TfOH: For the intramolecular arylation of two-carbon-tethered arylindole **1n** via the sole protonation of the C2=C3 bond, even if the $(TfOH)_2$ dimer is taken into account in the computations, the transition state of the C2 arylation leading to six-membered ring-fused indoline **16n** is lower in energy than the one of the C3 arylation delivering five-membered-ring spiroindoline **15n**. However, C3 arylation can be enforced by protonating the indole nitrogen atom, which prevents C3 protonation to avoid a 1,2-dication. The protonation then takes place at C2 and the C3 arylation benefits from a strong stabilization of the cationic intermediates and transition states by the highly polar environment offered by the H-bonded $(TfOH)_n$ cluster.[22,23]

Conclusion

We developed the regioselective dearomative inter- and intramolecular 3-hydroarylation of unbiased indoles leading to three-dimensional 3-arylindolines and five- or six-membered 3,3-spiroindolines which are biologically relevant structures. This redox-neutral addition of a nucleophile to the C3 position of N–H or *N*-alkyl indoles is very rare and is in sharp contrast with the usual C2-addition of a nucleophile to the transient C2-iminium generated by isomerization of the enamine moiety of N–H or *N*-alkyl indoles. This unique atom-economical transformation based on umpolung of indoles only requires triflic acid at room temperature, which makes this methodology operationally simple and practical. It strongly differs from known strategies since it does not require the introduction of a strong electron-withdrawing group or an oxidation event. A DFT investigation suggests the involvement of C3 cationic or 1,3-dicationic intermediates stabilized by H-bonded $(TfOH)_n$ clusters.

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the Supporting Information of this article.

Keywords: Dearomatization · Indoles · Indolines · Super Acids · Umpolung

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