Umpolung of Indoles: Triflic Acid-Mediated C3-Regioselective Hydroarylation of N-H Indoles

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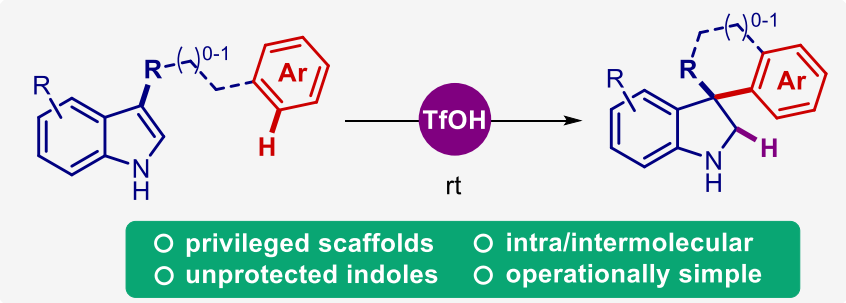
The direct dearomative addition of arenes to the C3-position of unprotected indoles is reported under operationally simple conditions, using triflic acid at room temperature. The present regioselective hydroarylation is a straightforward manner to generate an electrophilic indole at the C3-position without the need of a deactivating acetyl group at the indolic nitrogen as in previously reported 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.



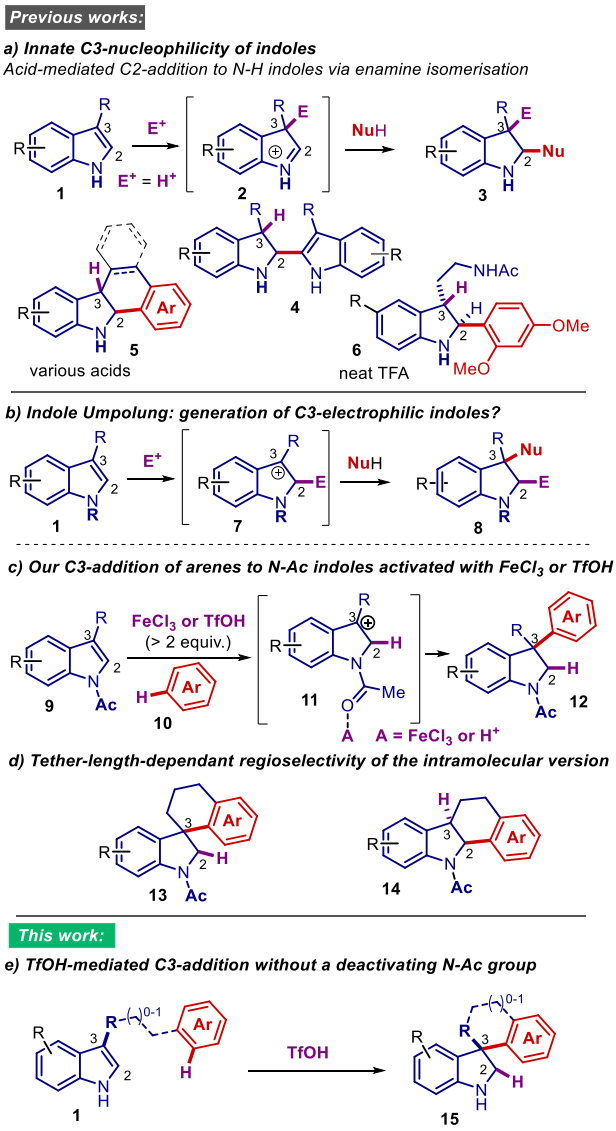
The indole nucleus displays a strong nucleophilicity at the C3-position,[1] allowing reactions with a range of electrophiles. In this context, addition of nucleophiles at the C2-position of N-H indoles **1** is possible under acidic conditions after protonation of the C3-position (E = H), leading to products **3** via the iminium species **2** (Scheme 1a).[3] This typical reactivity pattern has been widely exploited in dearomatization strategies.[2] 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**.[3a,c] The formation of compounds **5**, featuring a 6-membered ring, has also been reported by intramolecular addition of arene nucleophiles (such as indoles,[3b,c,d] anilines[3e] or pyrroles[3f,g]) to the C2-iminium intermediate. The intermolecular addition of a nucleophile[3h,i,k,m] has been more rarely achieved since it requires a more reactive species than the indole itself to prevent dimerization into **4**.[3a] For instance, the addition of 1,3-dimethoxybenzene at the C2-position of tryptamine derivatives into **6** was described by Laronze in trifluoroacetic acid.[3h] However, the regioselective nucleophilic addition to the C3-position of **1** to give **8** (via electrophilic intermediate **7**) appears to be mechanistically less favorable since it involves the reversal of the inherent reactivity of the indole ring (Scheme 1b).

Over the past decade, we have been interested in the Umpolung of indoles and we aimed at developing synthetic dearomatization methods that overturn this innate reactivity of the indole nucleus.[4,5] Based on preliminary findings from the group of Nakatsuka,[6] we reported the intermolecular regioselective C3-hydroarylation of 3-substituted *N*-Ac indole derivatives **9** by electron-rich arenes **10** in presence of typically more than 2 equivalents of $FeCl_3$, or TfOH (Scheme 1c).[7-9 10,11 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 **13** via the formation of a 6-membered ring,[8,12] while a two carbon linker favors the formation of 6-membered ring-fused indolines **14** by addition of the arene at the C2-position. Nevertheless, this expedient access to biologically relevant spiroindolines[13] contrasts with the classical dearomatizing methods[2] 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 simplify and generalize our synthetic method, we finally found that unprotected indoles **1** undergo intra- or intermolecular hydroarylations mediated by TfOH (Scheme 1e). In this paper, we report 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 **15** and provide a mechanistic rationale supported by DFT calculations.

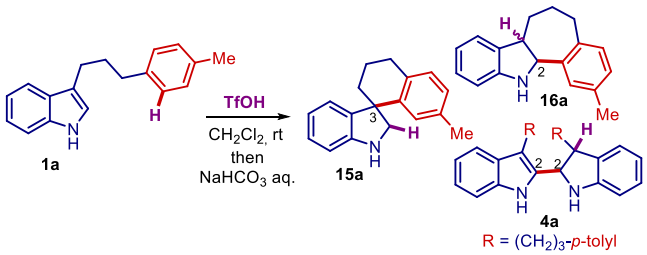
Scheme 1. Hydroarylation of electrophilic indoles



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.**[3a-g] Indeed, treating **1a** with 1.0 or 1.5 equivalents of TfOH mainly led to dimer **4a** (entries 1,2). 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 3).

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.

Table 1. Optimization of the intramolecular hydroarylation of indole 1a.[a]



Entry	Equiv. TfOH	NMR yield[b]		
		15a	**16a**	**4a**
1	1.0	0%	0%	80%
2	1.5	2%	0%	54%
3	2.5	99%	0%	0%

*a Reactions conditions: 0.05 mmol of **1a** and x equiv. of TfOH in 0.5 mL of CH2Cl2 at rt for 20 h followed by work-up with saturated aqueous NaHCO3; b determined by 1H NMR using CH2Br2 as internal standard.*

We next explored of the scope of this reaction to demonstrate its utility (Scheme 2). 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 at play in this second set of reaction conditions. Using a less electron-rich phenyl nucleophile required a much higher (20 equivalents) loading of triflic acid as promotor to deliver 5-methoxyspiroindoline **15h** (76%) and 5-chlorospiroindoline **15i** (99%).

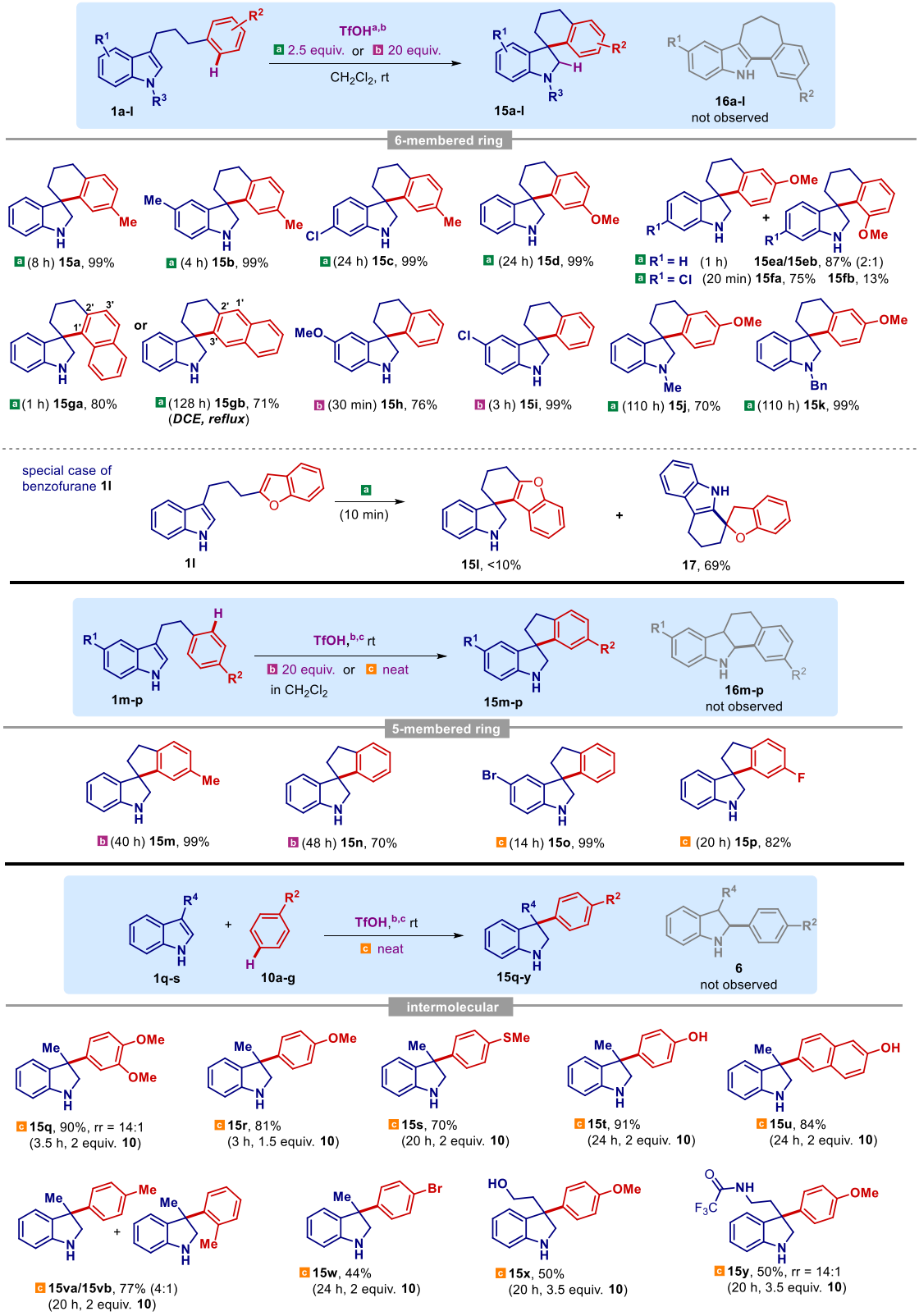
We then looked at the substitution of the indolic nitrogen and we were pleased to observed that both *N*-methyl and *N*-benzyl indoles were prone to deliver the respective spiroindolines **15j** (70%) and **15k** (99%), albeit in a significantly longer reaction time compared to the corresponding N-H 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 **18** was obtained as the major compound (69%). In this case, the benzofurane was probably more easily protonated than the indole ring, generating an electrophilic benzofurane cation onto which the indole moiety could add as a nucleophile.

We were also eager to study the reactivity of 2-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 6-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 2). 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**)[3b-g] including our own results with the corresponding *N*-Ac indoles (Scheme 1d; compounds **14**).[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 2-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[3a] and the previously reported addition of external nucleophiles occurred at the C2-position (Scheme 1a; compound **6**).[3h] Indeed, dimerization of 3-methylindole is mainly observed with a stoichiometric amount of TfOH in CH_2Cl_2. 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.[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,y**.

Scheme 2. Scope of the TfOH-mediated C3-regioselective hydroarylation of indoles.

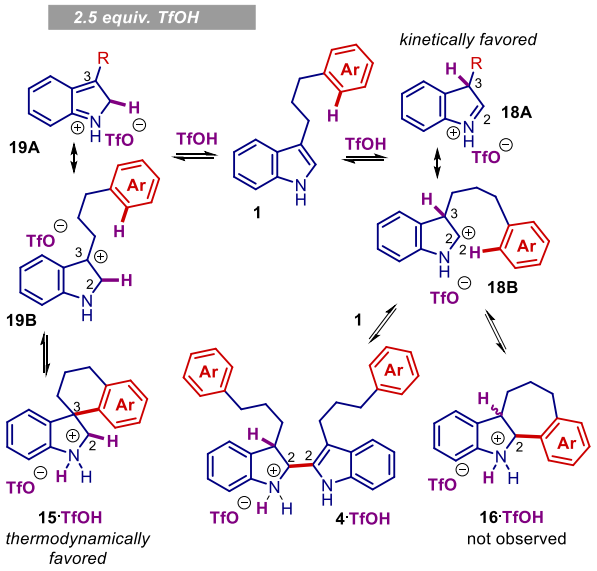


*Reactions conditions: 0.1 mmol of **1a-p** (intramolecular) or 0.25 mmol of **1q-s** (intermolecular) and 2.5 equiv. TfOH (conditions a), 20 equiv. TfOH (conditions b) in 1 mL of CH_2Cl_2 or in pure TfOH (0.5 mL, conditions c) at rt, followed by work-up with saturated aqueous $NaHCO_3$ (rr = regioisomeric ratio, rr > 14:1 unless otherwise noticed).*

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-aryl-indolines **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 C3-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].

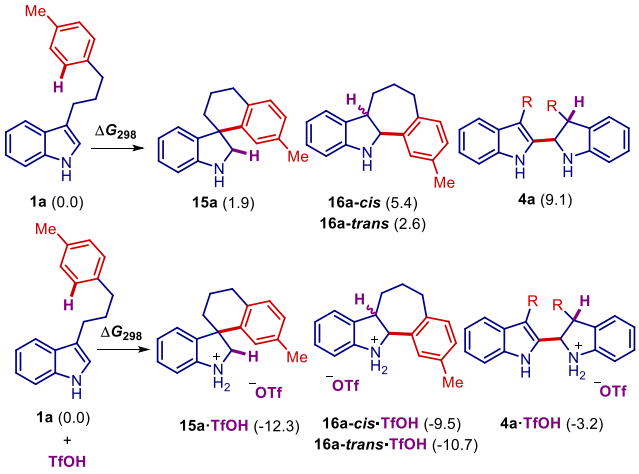
To explain the exquisite regioselectivity of the reaction towards C3-arylindolines **15** without observing intramolecular additions of the arene group to the C2-position, we first elaborated the following mechanistic hypothesis for the formation of the 6-membered 3,3-spiroindolines **15a-k** in presence of 2.5 equivalents of TfOH (Scheme 3). 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.

Scheme 3. Mechanistic hypothesis for the C3-intramolecular hydroarylation leading to 6-membered spiroindolines 15a-l.



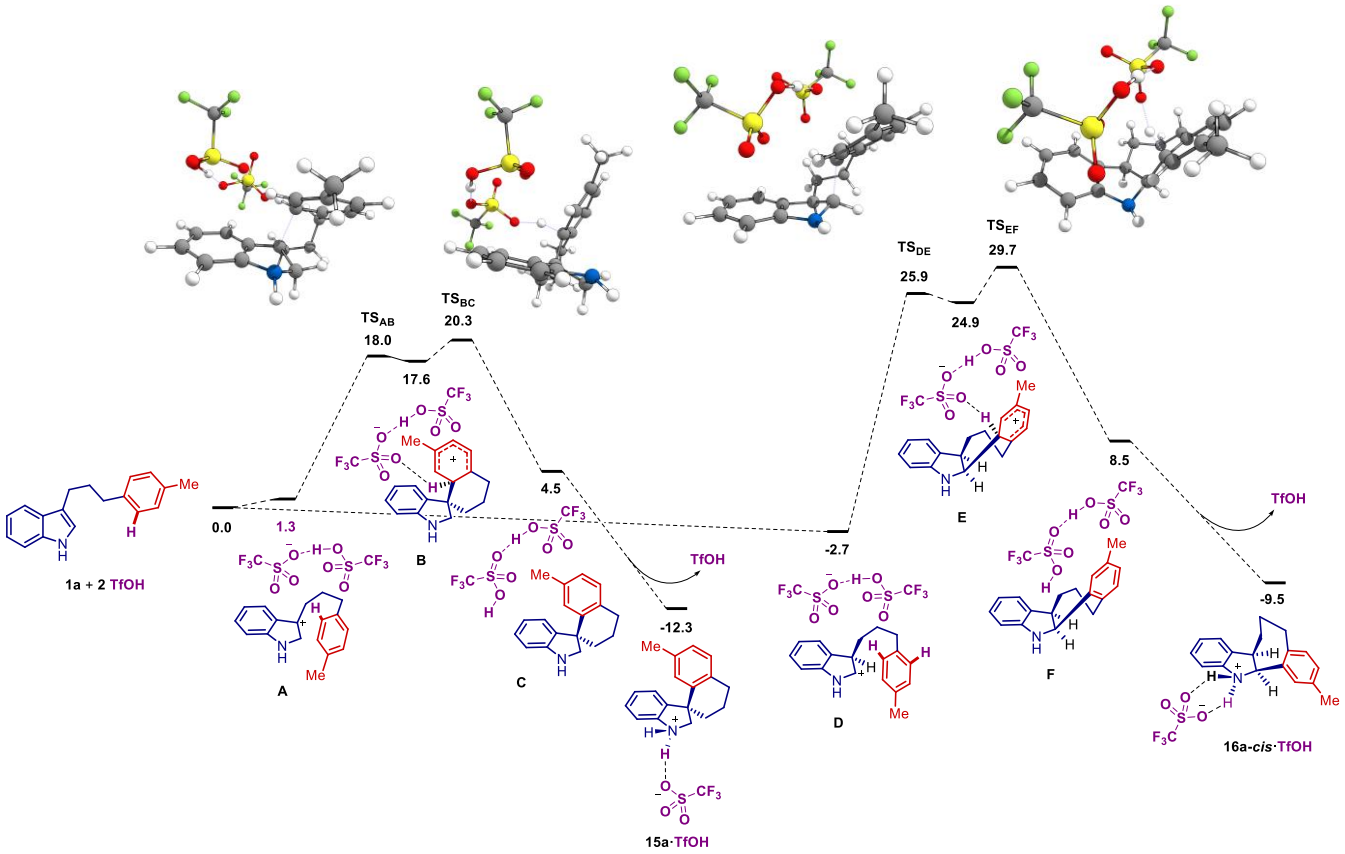
To gain more insights, we performed a DFT study, which is fully described in the Supporting Information. Geometries were optimized at the M06-2X level of theory. All atoms were described by the 6-311+G(d,p) basis set. The values discussed are Gibbs free energies (ΔG_{298}, kcal/mol) including PCM solvation correction. The 3-carbon-tethered arylindoles **1a** and the 2-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 4). 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, 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* 7-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 $NaHCO_3$.

Scheme 4. Free energy of the products from 3-carbon-tethtered indole 1a (ΔG_{298}, kcal/mol; R = $(CH_2)_3$-*p*-tolyl).



We then studied the reaction pathways. By using one explicit TfOH molecule in the computations (not shown, see the SI for details), we found that the kinetically favored pathway is the formation of the dimer **4a·TfOH**, but it is easily reversible. The spiro derivative **15a·TfOH** is favored thermodynamically over all species (Scheme 4), but also kinetically over the 7-membered ring products (TS of 26.0 kcal/mol). While in line with the experimental results for **1a**, at 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 equiv 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 Figure 1 (left part).

Figure 1. Free energy profile for the formation of **15a·TfOH** and **16a-*cis*·TfOH** using 2 equiv of TfOH (ΔG_{298}, kcal/mol); geometries of the transitions states (blue = N; red = O; yellow = S; green = F).

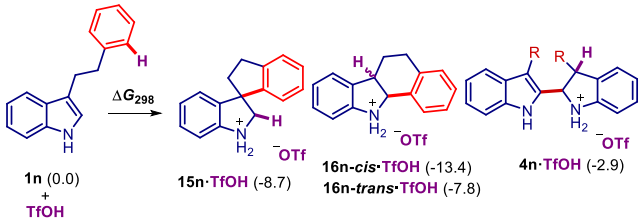


Protonation at C2 to give **A** is endergonic by 1.3 kcal/mol. Nucleophilic attack of the *p*-tolyl group to the carbocationic center takes place through **TS$_{AB}$**, lying at 18.0 kcal/mol on the free energy surface. It leads to the Wheland-type intermediate **B** at 17.6 kcal/mol. Deprotonation is the rate-determining step, **TS$_{BC}$** being found at 20.3 kcal/mol. As discussed above, the corresponding spiro derivative **C** is less stable than the reactants (by 4.5 kcal/mol 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. In contrast with the C2 protonation, the protonation at C3 is exergonic (Figure 1, right part: **D**, -2.7 kcal/mol). 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; $\mathbf{TS_{EF}}$ 29.7 kcal/mol). 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 2-carbon-tether indole **1n** indicated that the related pathway via the sole protonation of the C2=C3 bond favored the cyclization at C2 into 6-membered ring fused indoline **16n·TfOH** over cyclization at C3 into 5-membered spiroindoline **15n·TfOH** even with two explicit TfOH molecules. 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 5).

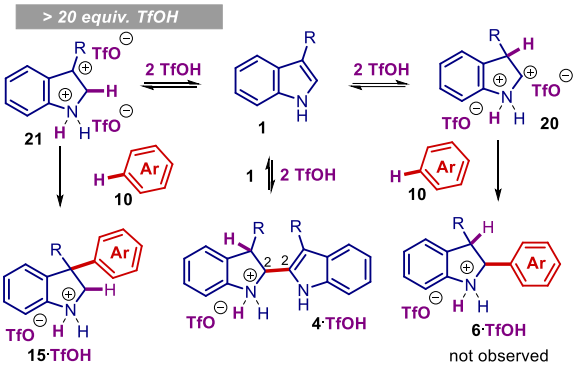
Scheme 5. Free energy of the products from 2-carbon-tethtered indole 1n (ΔG_{298}, kcal/mol; R = $(CH_2)_2$-Ph).



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

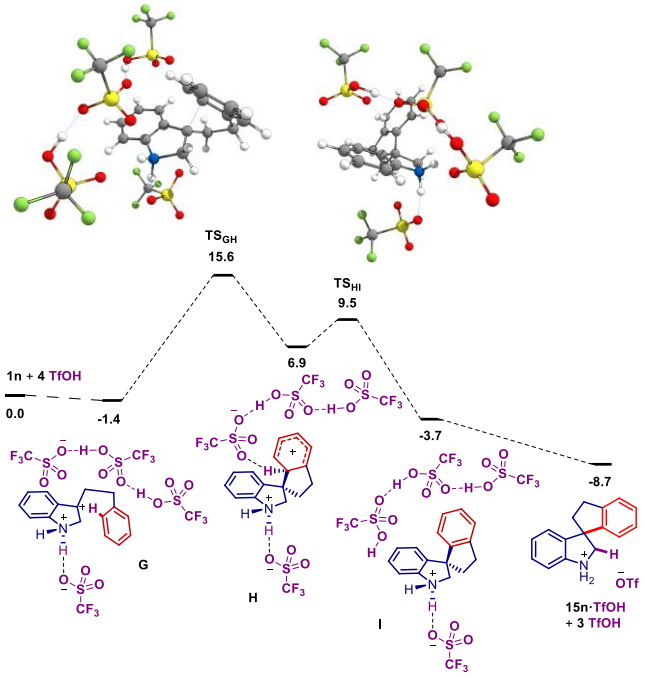
To account for the formation of **15n-y** in the presence of a large excess of acid, an alternative mode of activation of the indole with TfOH was therefore investigated. In these superacidic conditions, superelectrophilic species could be generated.[23,24] Double protonation of the indole might occur at both the nitrogen position and at C2 or C3, leading respectively to diprotonated species **20** and **21** (Scheme 6). 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 this pathway, only the 3-arylated indolines **15·TfOH** would be obtained after C2 protonation (1,3-dication **21**) and addition of arene **10**.

Scheme 6. Mechanistic hypothesis for the regioselective inter- and intramolecular C3-hydroarylation leading to indolines 15q-l and 5-membered-ring spiroindolines 15m-p.



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 6-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.[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 (Figure 2).[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), 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. The corresponding Wheland intermediate also enjoys a strong stabilization (**H**; 6.9 kcal/mol) and the deprotonation transition state could be found only 2.6 kcal/mol above it ($\mathbf{TS_{HI}}$; 9.5 kcal/mol). 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.

Figure 2. Free energy profile for the formation of **15n·TfOH** in the presence of 4 molecules of TfOH (ΔG_{298}, kcal/mol); geometries of the transitions states (blue = N; red = O; yellow = S; green = F).



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 preferred 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*) *Reactions with 2.5 equiv of TfOH*: For intramolecular arylations of 3-carbon-tethered arylindoles **1a-l**, the formation of a 6-membered ring is entropically favored over a 7-membered ring one. Thus, the 6-membered ring pathway leading to a spiro derivative **15a-l** 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. For intramolecular arylations of 2-carbon-tethered arylindoles **1m-p**, the formation of a 6-membered ring can only result from a C2-arylation. However, even if the $(TfOH)_2$ dimer is taken into account in the computations, a high barrier is expected.

(*ii*) *Reactions with ≥ 20 equiv of TfOH*: For intramolecular arylations of 2-carbon-tethered arylindoles **1m-p** and intermolecular reactions of **1q-s**, 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]

In conclusion, we demonstrated that the regioselective dearomative inter- and intramolecular 3-hydroarylation of indoles could be performed without the need of a deactivating acetyl group and leads efficiently to the 3-arylindolines and 5- or 6-membered 3,3-spiroindolines. 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. 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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(25) For compound **1a** leading to 6-membered ring spiroindoline **15a**, the pathway via a 1,3-dication such as **21** involving two molecules of triflic acid (one to protonate the indolic nitrogen and one to protonate the C2-position) has an activation barrier of 45 kcal/mol which compares very unfavorably to the C3-monocation pathway with a $(TfOH)_2$ cluster described in Figure 1.