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

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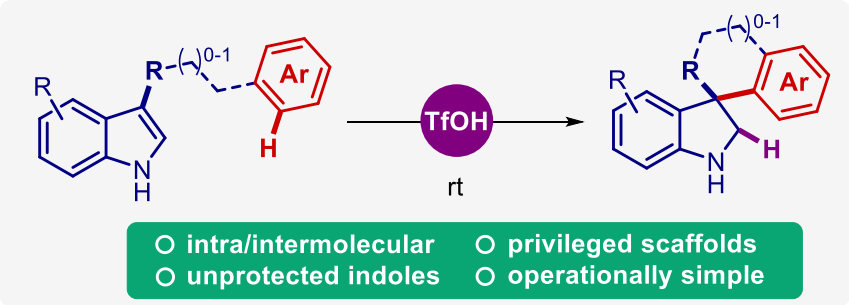


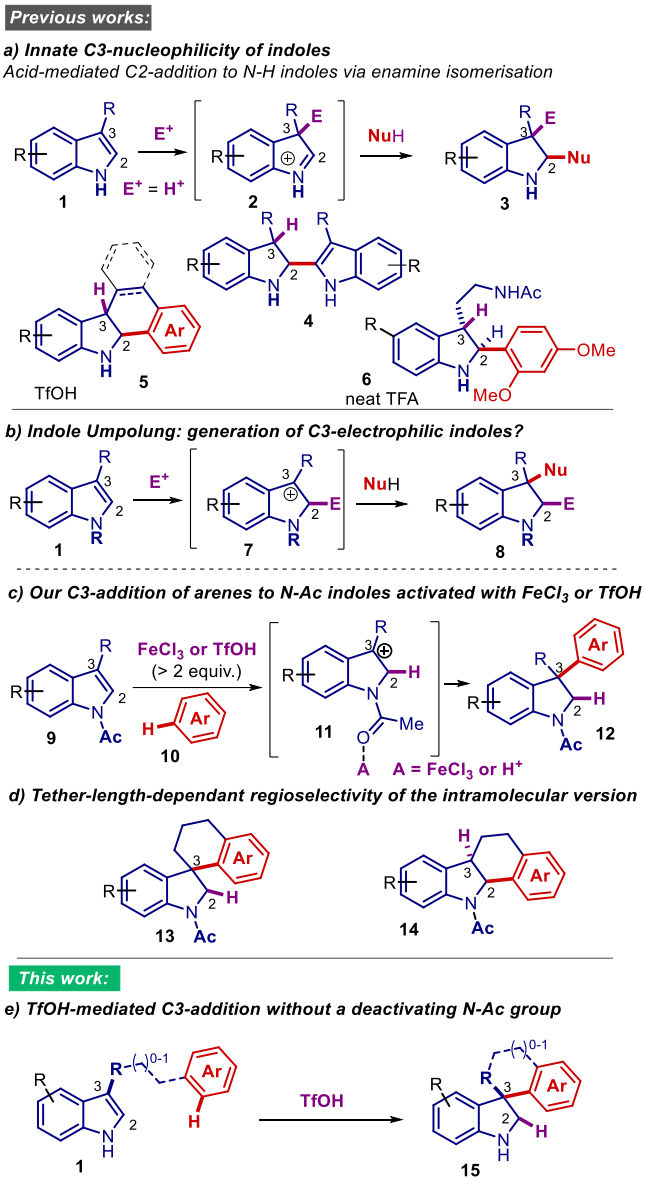

The direct dearomative addition of arenes to the C3-position of unprotected indoles is reported under operationally simple conditions with triflic acid at room temperature. The present regioselective hydroarylation is a straightforward manner to generate an electrophilic indole at the C3-position without the need to introduce a deactivating acetyl group on the indolic nitrogen as in previously reported strategies. This atom economy method delivers biologically relevant 3-aryl indolines and 3,3-spiroindolines in high yields and regioselectivities from both intra and intermolecular processes.

The indole nucleus displays an intrinsic strong nucleophilicity at its C3-position,[1] allowing reactions with a range of electrophiles which, indeed, have been exploited in dearomatization reactions.[2] In this context, additions of nucleophiles have been reported to the C2-position of N-H indoles **1** in acidic conditions via protonation of the C3-position (E = H) and isomerization of the enamine moiety into an iminium species **2** leading to products **3** (Scheme 1a).[3] Thus, dimerization of N-H indoles **1** into dimer **4** are often observed, in which one indole **1** acts as nucleophile to add at the C2-position of iminium intermediate **2**.[3a,c] The formation of compounds **5**, featuring a 6-membered ring, are also reported by intramolecular addition of arene nucleophiles (such as indoles,[3b,c,d] anilines[3e] or pyrrole[3f,g]) to the C2-iminium intermediate. The intermolecular addition of a nucleophile[3h,i,k,m] has been more rarely reported since it required a more reactive external nucleophile than 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 trifluoro acetic acid.[3h] However, the corresponding regioselective nucleophilic addition to the C3-position of **1** into **8** (via electrophilic intermediate **7**) appears to be mechanistically less obvious since it involves the reversal of the inherent reactivity of the indole ring (Scheme 1b).

For the last 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 stoichiometric amounts of 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 led to 3,3-spirocyclic indolines **13** via formation of a 6-membered ring,[8,12] while a two carbon linker favored the formation of 6-membered ring-fused indoline **14** by addition of the arene at the C2-position. Nevertheless, this strategic access to biologically relevant spiroindolines[13] contrasts with the classical approaches via dearomatizing methods[2] relying on the classical 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 afterwards usually necessitates rather strong conditions (aq. HCl, EtOH, 85 °C).

Aiming to improve and simplify our synthetic system, we found out 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**.

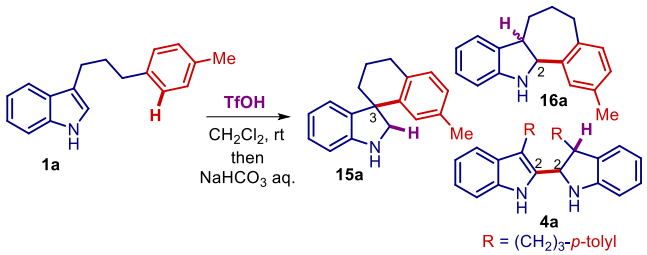
**Scheme 1. Hydroarylation of electrophilic indoles**




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

Hence, this finding led us to the conlusion that the *N*-Ac deactivating group seems not mandatory to orientate the regioselectivity of the hydroarylation at C3-position. *This discovery represents a major practical and conceptual advance*: in addition to avoid the undesirable introduction and removal of the acetyl group, it also demonstrates that the delocalization of the nitrogen lone pair into an electron withdrawing group is not essential to generate the C3-electophilicity 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 $CH_2Cl_2$ at rt for 20 h followed by work-up with saturated aqueous $NaHCO_3$; [b] determined by $^1H$ NMR using $CH_2Br_2$ as internal standard.

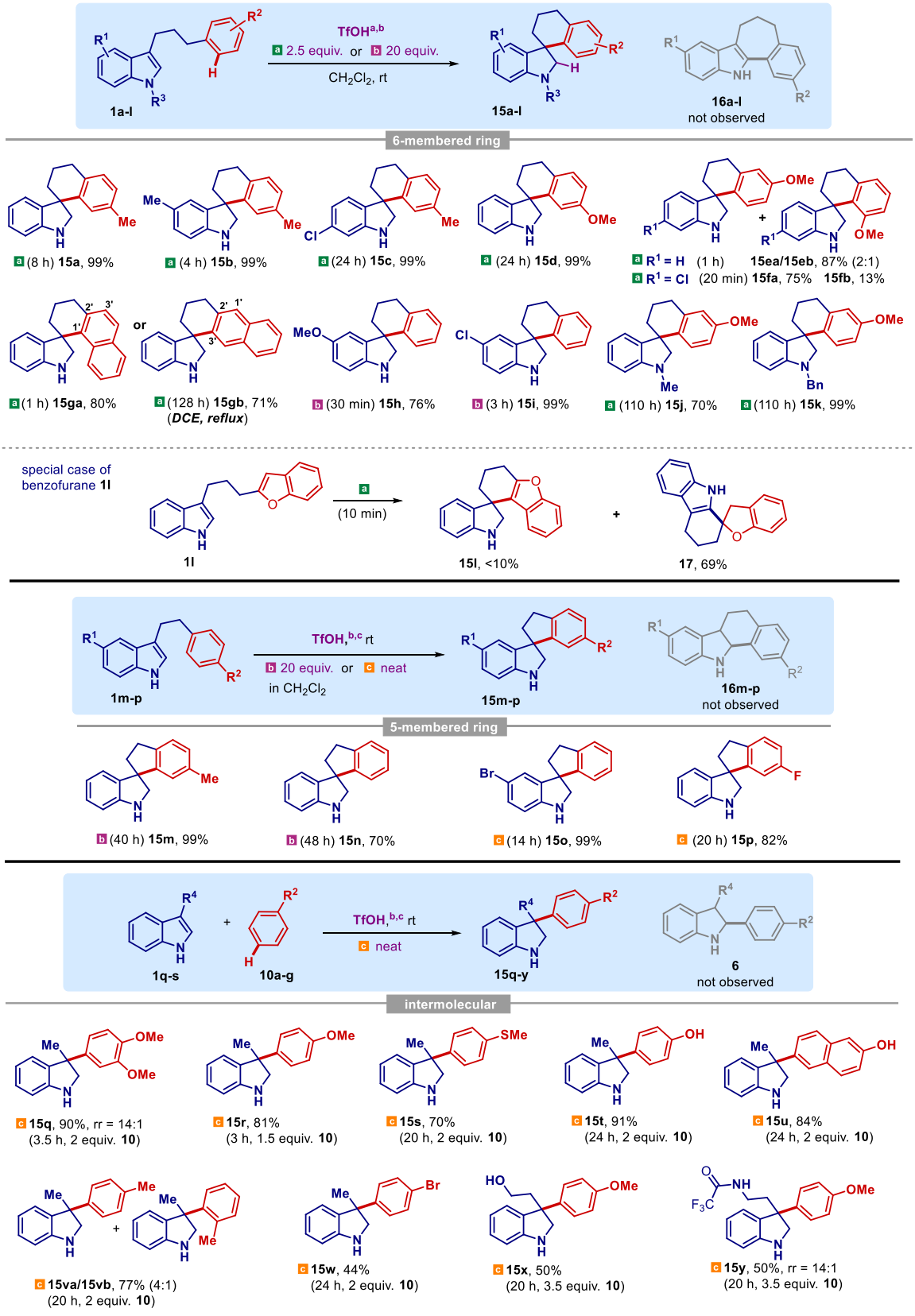
We next embarked in a study of the scope of this reaction to demonstrate its utility (Scheme 2). Indeed, compound **15a** could be isolated in 99% yield with 2.5 equivalents of TfOH. Electron-richer and electron-poorer indoles also proved to be reactive, leading to 5-methyl and 6-chloro spiroindolines **15b** and **15c** in 99% yield. The nature of the nucleophilic arene was then studied. Switching from a *para*-tolyl group to a *para*-anisyl 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 one hour to spiroindoline **15ga** (80%). Interestingly, performing this reaction in refluxing dichloroethane for a prolonged reaction 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 kinetic product **15ga** to thermodynamic one **15gb** is at play in the 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 spioindolines **15j** (70%) and **15k** (99%) albeit in a significantly longer reaction time than the corresponding N-H indoles. Interestingly, 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 on 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 term of reactivity and regioselectivity. As already mentioned and observed, N-H-indoles have a high propensity to dimerize in 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 the intermolecular hydroarylation of 3-methylindole with the addition of veratrole at the C3-position leading to **15q**. Once again, this C3-regioselectivity is in sharp contrast to what has been observed previously (Scheme 1a). Anisole, thioanisole, phenol, 2-naphtol and toluene were also competent nucleophiles in 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-catalyzed C3-regioselective hydroarylation of indoles.**

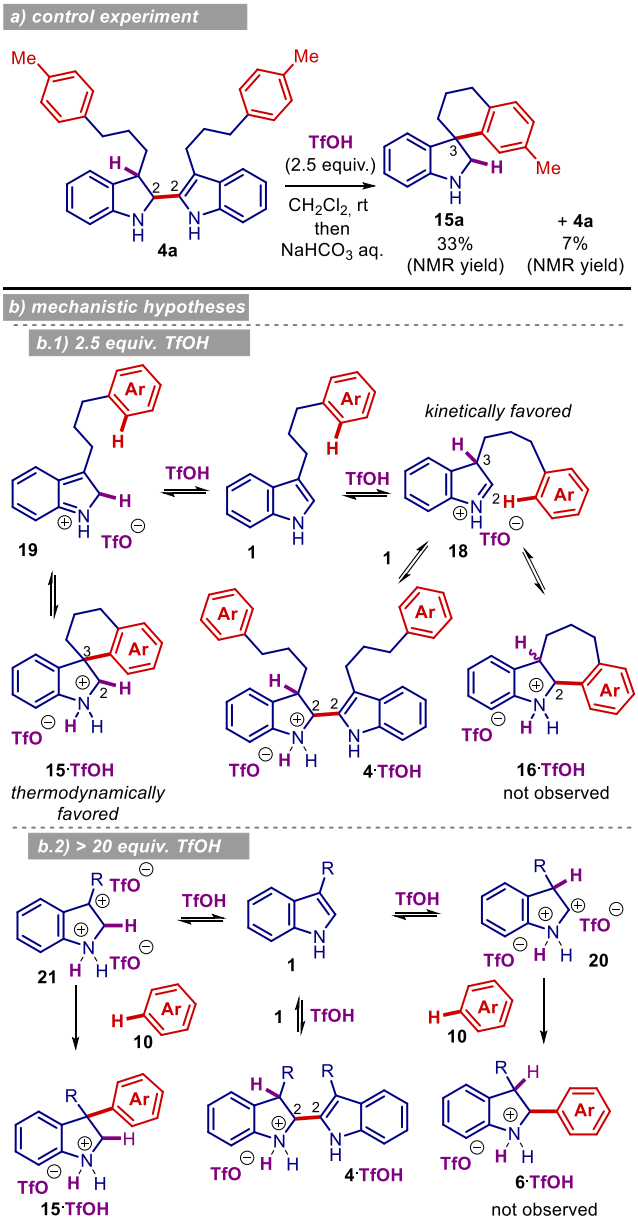



Reactions conditions: 0.1 mmol of **1a-p** (intramolecular) or 0.25 mmol of **1q-s** (intermolecular) and 2.5 equiv. TfOH (conditions a), 20 equiv. TfOH (conditions b) in 2 mL of $CH_2Cl_2$ or in pure TfOH (0.5 mL, conditions c) at rt, followed by work-up with saturated aqueous $NaHCO_3$ (rr = regioisomeric ratio, rr > 14:1 unless otherwise noticed).

From a mechanistic point of view, the effect of the stoichiometry of TfOH (Table 1) on the formation of either 3,3-spiroindoline **15a** or dimer **4a** seems to indicate that the latter is reversible and that an excess of triflic acid drives the reaction towards **15** as the most stable product via the regeneration of **14**. To confirm this hypothesis, a control experiment was performed by treating dimer **4a** with an excess of triflic acid, which led to the formation of 3,3-spiroindoline **15a** (Scheme 3a). This led us to establish the following mechanistic hypothesis for the formation of 6-membered rings 3,3-spiroindolines **15a-k** in presence of 2.5 equivalents of TfOH. In the presence of a stoichiometric amount of triflic acid, protonation at the C3-position of the enamine moiety of N-H indole **1** into iminium **18** would likely be kinetically favored over C2 protonation into **19** (Scheme 3b). Intermolecular Friedel-Crafts reaction of **18** with another molecule of indole **1** leads to dimer **4.TfOH** as a triflic salt. However, an excess of triflic acid could promote a retro Friedel-Crafts reaction of **4.TfOH**, regenerating **1** via **18**. Reversible protonation of **1** could also generate extended iminium **19** and its electrophilic position at C3 could be intramolecularly trapped into 3,3-spiroindoline triflic acid salt **15.TfOH**, which is believed to be the thermodynamically favored product. Overall, despite a protonation equilibrium probably lying mainly on the C3 side, the minor C2-protonated species **19** is the main productive species in excess of TfOH.

In contrast, the cyclization into the 5-membered-ring 3,3-spiroindolines **15m-p** and the intermolecular reaction leading to indolines **15q-y** require a very large excess of TfOH (20 equivalents or more).[15] In these superacidic conditions, superelectrophilic species could be generated. 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**. Carbocation charge at the benzylic C3-position of **21** seems to be more favored than the C2-position of **20**. Addition of arene **10** to **21** would then lead to 3-aryl indoline triflic salt **15.TfOH**.

**Scheme 3. Mechanistic insights.**



These atypical C2-protonations of indoles have been known from 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 demonstrated the coordination of Au(I) complexes at C2-position.[19] Overall, reactions triggered by direct nucleophilicity of C2 of indoles may often be underestimated, as shown by recent studies.[20]

In conclusion, we demonstrated that the regioselective dearomative inter- and intramolecular 3-hydroarylation of indoles could be effected without the need of an activating acetyl group and lead efficiently to the 3-aryl indolines and 5- or 6-membered 3,3-spiroindolines. This redox-neutral addition of a nucleophile into 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 delocalization of the nitrogen lone pair of N-H or N-alkyle indoles. This unique Umpolung of indoles and atom economy transformation only requires triflic acid at room temperature, which makes this methodology operationally simple and practical.

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