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"Back-to-Front" Indole Synthesis Using Silver(I) Catalysis: Unexpected C-3 Pyrrole Activation Mode Supported by DFT

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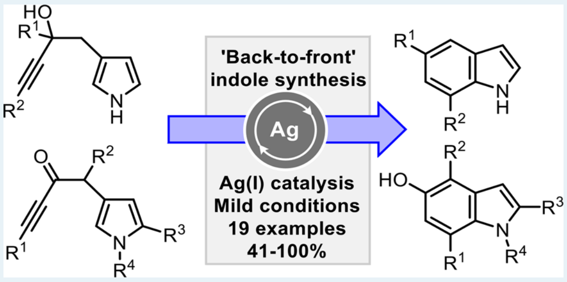
Supporting Information

ABSTRACT: An efficient silver(I)-catalyzed method is reported for the synthesis of substituted indoles, most notably 5-hydroxy-derivatives, via π-acidic alkyne activation. Most methods for the preparation of indoles involve annulation of a benzene precursor, but the method reported herein is unusual in that pyrrole precursors are used. Density Functional Theory (DFT) studies suggest that these reactions proceed via initial activation of the pyrrole C-3 position before undergoing subsequent rearrangement, contradicting the conventional wisdom that pyrroles are more nucleophilic through C-2.



KEYWORDS: *indoles, alkynes, silver(I), cyclization, spirocycles*

INTRODUCTION

Indole derivatives are crucial in human biology (Figure 1); for example, tryptophan **1** is an essential amino acid, and serotonin **2** and melatonin are neurotransmitters.[1,2] Indoles are also ubiquitous in the plant world, and they are important components of agrochemicals, functional polymers/sensors, fragrances, and dyes. However, the significance of indole derivatives (especially 5-hydroxy indoles) is best highlighted by their biomedical applications (Figure 1).

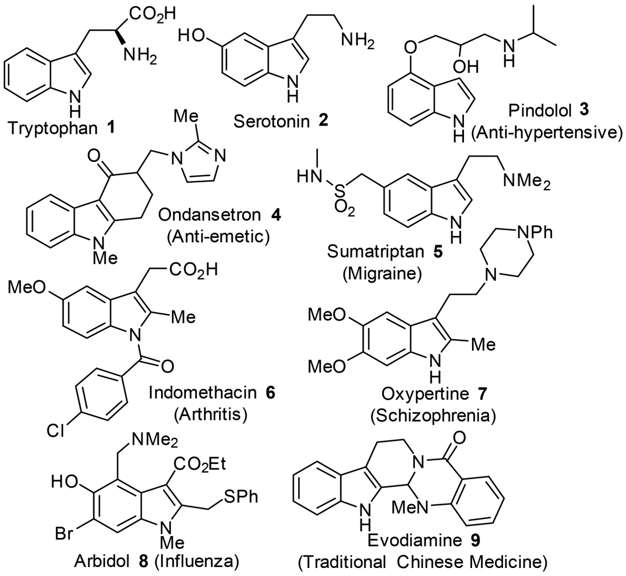


Figure 1. Biologically important indole derivatives.

As well as well-known natural products such as the anticancer vinca alkaloids (vincristine/vinblastine) and tranquilizing reserpine alkaloids, major indole-based drugs include pindolol (**3**, antihypertensive), ondansetron (**4**, antiemetic), Sumatriptan (**5**, migraine), indomethacin (**6**, arthritis), oxypertine (**7**, schizophrenia), and Arbidol (**8**, influenza).[1,2] Furthermore, many more indoles with high pharmaceutical potential are in the pipeline, for example, evodiamine **9**[3] and dragmacidin D.[4]

The range of applications of indole derivatives has stimulated much research into the search for efficient methods for their synthesis.[1,5,6] As can be seen from Figure 1, versatile synthetic approaches are needed in terms of substituent variation. Such a synthetic challenge, with such valuable targets, ensures that novel approaches to indole synthesis are continually being reported.[1,5−7] Of course, the Fischer indole synthesis,[6] in which a phenylhydrazine is treated with an aldehyde or ketone, is still enormously important both in small scale and in industrial procedures. The vast majority of subsequently developed procedures also employ arylhydrazines, anilines, nitrobenzenes, or related benzene derivatives, and we have termed these the "standard" (or "front-to-back") approaches, with many being named reactions (Scheme 1a).

In contrast, there are far fewer indole syntheses that commence from pyrrole or substituted pyrroles (Scheme 1b), and those that are known often afford little scope for substituent variation.[8,9] The Muratake−Natsume indole synthesis (a Friedel−Crafts-type approach) is perhaps the only established named reaction of this type,[8a] although a few other more recent procedures have also been reported.[9]

The research described herein concerns the development of new silver(I)-catalyzed, pyrrole-based routes to indoles, of the

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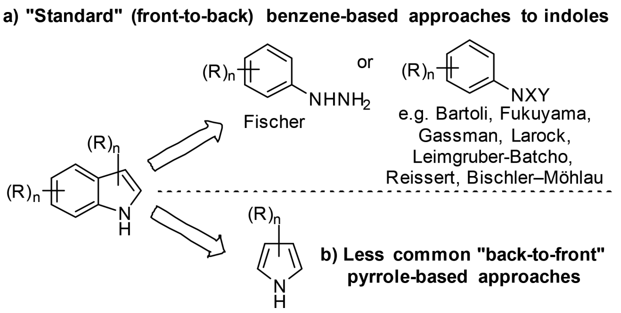
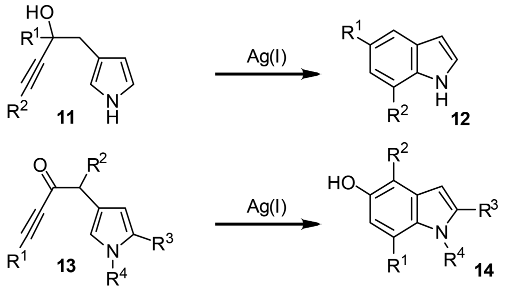
Scheme 1. Standard (a) and “Back-to-Front” (b) Approaches to Substituted Indoles[6−9]



rare “back-to-front” type, as outlined in Scheme 1b. We have recently developed a number of efficient metal-catalyzed ynone and ynol cyclization procedures for the synthesis of various cyclic scaffolds, including spirocyclic indolenines,[10,11] other spirocycles,[10a,d,12] carbazoles,[10b,c] quinolines,[10b,e] and quinolizidines.[13] In this Article, two new silver(I)-catalyzed procedures for the conversion of ynols **11** into indoles **12**, and ynones **13** into 5-hydroxy-indoles **14**, are reported (Scheme 2). Both approaches can be used to prepare indoles with a range of substitution patterns from closely related starting materials. Furthermore, they are simple to perform and use mild reaction conditions, and hence represent a practical and versatile new approach to these important scaffolds. The reactions were also studied using Density Functional Theory (DFT), and, intriguingly, these studies suggest that the reactions proceed via initial cyclization at the pyrrole C-3 position before undergoing subsequent rearrangement, contradicting the conventional wisdom that pyrroles are more nucleophilic through C-2.

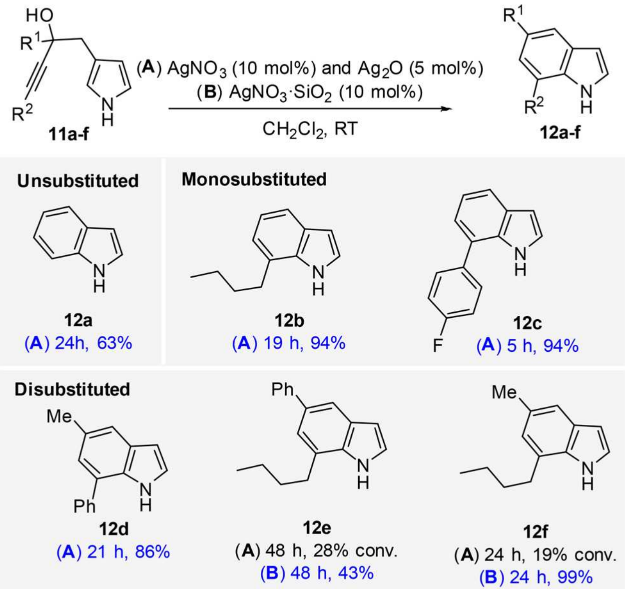
Scheme 2. “Back-to-Front” Ynol/Ynone Cyclization Approaches to Substituted Indoles



■ RESULTS AND DISCUSSION

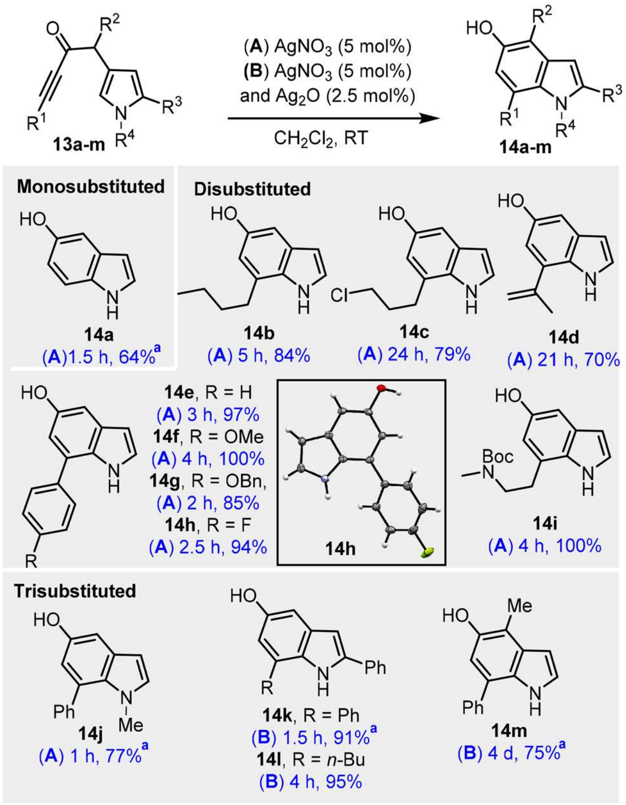
We started by examining the cyclizations of ynol derivatives **11a−f** (Scheme 3). The requisite starting materials (as well as ynones **13a−o** discussed later) were all prepared by standard literature procedures or minor variations thereof,[14] with full experimental and characterization details included in the Supporting Information. First, it was found that pyrrole **11a** ($R^1 = R^2 = H$) could be converted into unsubstituted indole **12a** in reasonable yield upon stirring with 10 mol % $AgNO_3$ and 5 mol % Ag_2O for 24 h at rt in CH_2Cl_2; these conditions were chosen as they had been shown to be effective for the cyclization of indole-tethered ynols in our earlier work.[10b] Monosubstituted indoles **12b** and **12c** were also formed in high yield using the same $AgNO_3$/Ag_2O conditions. Disubstituted indole **12d** was also formed in high yield in the same way, but these conditions were less successful for the formation of disubstituted indoles **12e** and **12f** (just 28% and 19% conversion, respectively, under the same conditions). However, using a silica-supported $AgNO_3$ catalyst ($AgNO_3 \cdot SiO_2$), which was developed as part of our earlier work on alkyne activation,[10d] the desired products were isolated in 43% and 99% yield, respectively. The role of Ag_2O in these reactions is not entirely clear; Ag_2O has been shown to improve reaction turnover when included as an additive in related Ag(I)-mediated cyclization reactions[10b] (as observed in this study), but it is not catalytically active in its own right; for example, ynol **11c** did not react when treated with 15 mol % Ag_2O under the standard reaction conditions. Thus, the role of this basic additive may instead be to modulate the acidity of the reaction (e.g., by quenching any adventitious protic acids present in the reaction), which may help prevent unwanted side reactions and/or catalyst degradation.[10b] Alternatively, its basicity may help to drive the dehydration step.

Scheme 3. Ynol Cyclization to Indoles 12a−f



Next, attention turned to the reactions of ynone derivatives of the form **13** (Scheme 4). These cyclization reactions are arguably of greater importance due to the fact that a 5-hydroxy substituent is produced in the product **14**; 5-hydroxylated indoles are ubiquitous in nature (e.g., serotonin **2**/indomethacin **6**), and this method could be used to generate analogues of these important compounds.[15] The hydroxy group may also serve as a reactive handle to enable further chemical modifications, for example, alkylation, cross-coupling, etc. First, simple 5-hydroxy indole **14a** was formed in 64% yield using 10 mol % $AgNO_3$ as catalyst, again upon stirring for 1.5 h at rt in CH_2Cl_2, with the Ag_2O additive not being necessary in this case. The Ag_2O additive was also not needed during the formation of disubstituted indoles **14b−i**, and the catalyst loading of $AgNO_3$ could also be lowered to 5 mol %. The yields were consistently high across this series, with aliphatic and electron-rich/electron-poor aromatic groups being well tolerated, as were tethered alkyl chloride and protected amine substituents. In the case of indole **14h**, its structural assignment is supported by X-ray crystallographic data.[16] Finally, four trisubstituted indoles **14j−m** were also

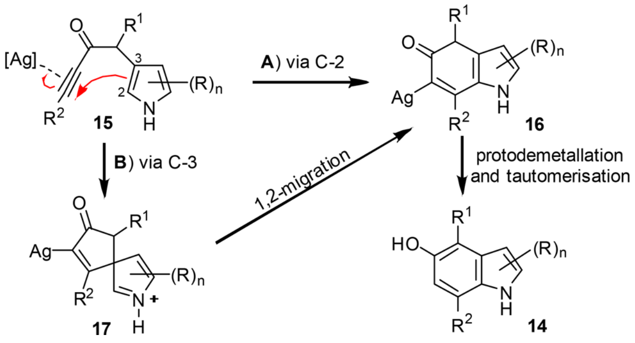
Scheme 4. Ynone Cyclization to Indoles 14a−m[a]



[a] Double the standard catalyst loading was required to achieve full conversion in this case.

generated; these substrates generally reacted more slowly than their disubstituted analogues, and some required the addition of Ag_2O to proceed to completion, but nonetheless each was formed in high yield under these modified conditions.

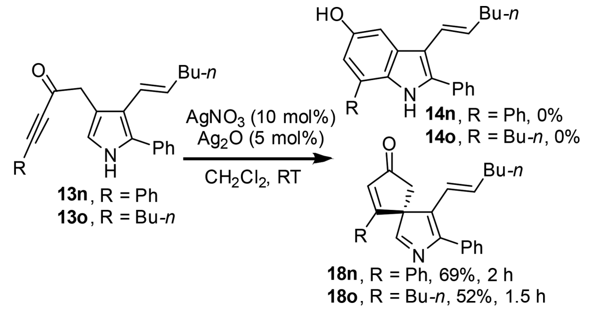
Scheme 5. Mechanistic Possibilities



In terms of the mechanism for these cyclization reactions, two main pathways were considered, illustrated in Scheme 5 for the ynone series. First, coordination of the alkyne to the active π-acidic silver species[17,18] increases its electrophilicity and activates it toward attack from the electron-rich pyrrole ring, either via the pyrrole C-2 position (**15** → **16**) or via its C-3 position (**15** → **17**). Cyclisation via C-2 (route A) was considered to be the most likely at the outset of this study, in view of the well-accepted wisdom that pyrroles are more nucleophilic through C-2 than C-3, and the fact that this was judged to be the less sterically encumbered of the two alternative pathways. Attack via C-2 is also the most direct route to the product, and thus from intermediate **16**, protodemetalation and tautomerization completes the reaction to form indole **14**. A second possibility, which was considered less likely in view of the above, but could not be ruled out, was that cyclization proceeds via C-3 (route B) to form a spirocyclic intermediate of the form **17**, before undergoing 1,2-migration (**17** → **16**), followed by protodemetalation and tautomerisation as in route A. For the ynol series, the same mechanism is likely to operate, except that the tautomerization step is replaced by the elimination of water (not shown).

However, subsequent examples led us to question our notion that C-2 cyclization is the more favorable pathway. Thus, when each of ynones **13n** and **13o** were reacted with 10 mol % $AgNO_3$ and 5 mol % Ag_2O at rt in CH_2Cl_2, none of the expected indole products **14n** and **14o** were formed, and instead spirocycles **18n** and **18o** were isolated (Scheme 6).

Scheme 6. Dearomatizing Spirocyclization Reactions of Ynones 13m and 13n

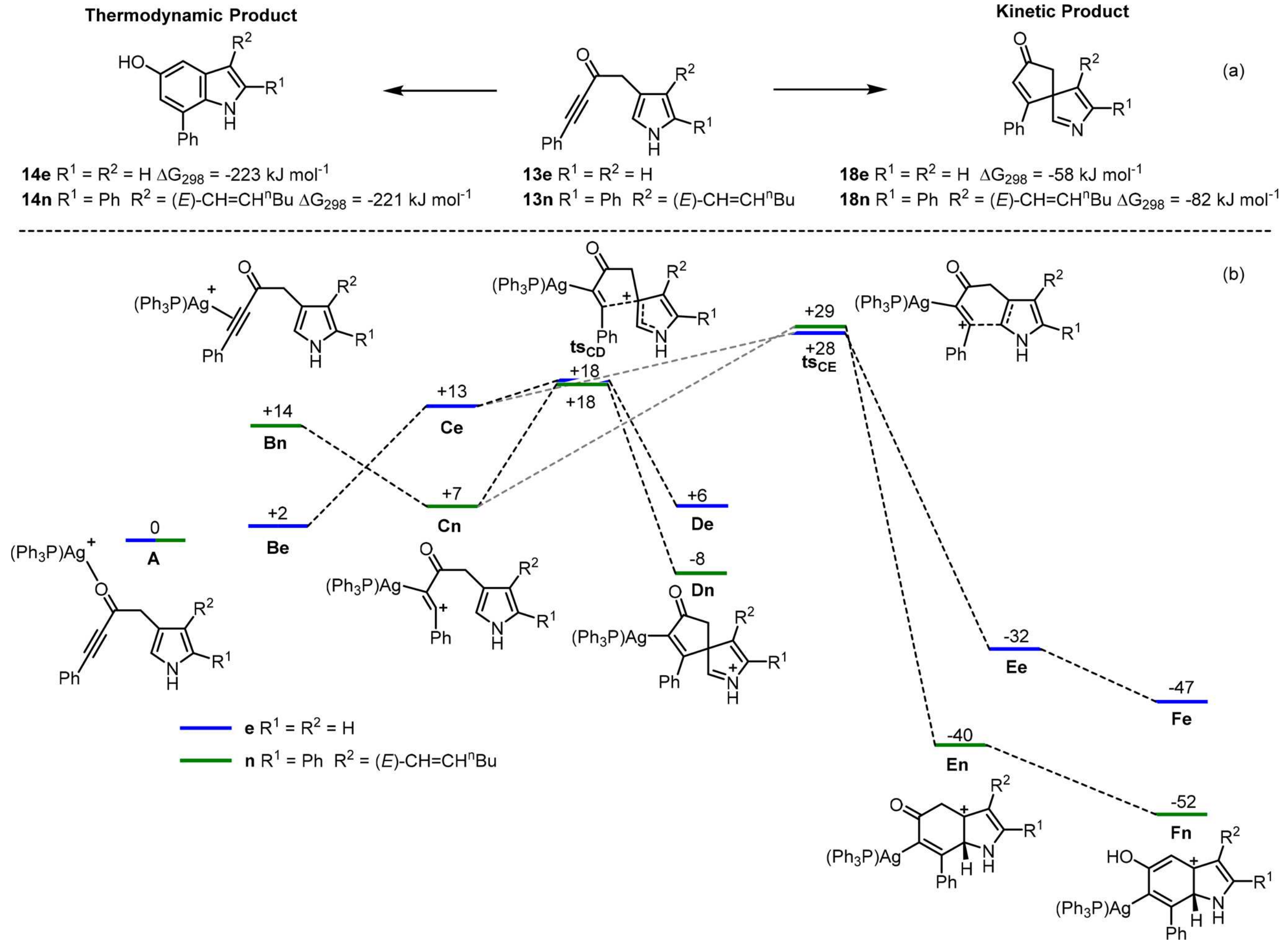


These results were surprising, not only because dearomatizing spirocyclization reactions through pyrrole C-3 positions are rare,[19,20] but also because spirocyclization had taken place in preference to C-2 annulation. Resubjecting the spirocyclic products **18n** and **18o** to the reaction conditions led to no discernible reaction (when 1,2-migration to convert them into **14n** and **14o**, respectively, might have been expected), even when heated to reflux, attesting to their surprising stability.

To gain a better understanding of the potential mechanistic pathways underpinning the silver-catalyzed reactions, a number of possible pathways for C−C bond formation were probed with Density Functional Theory (DFT, see the Supporting Information for details of the computational methodology employed).[21] Thus, one example from the "normal" indole-forming series (**13e** to **14e**) was examined and compared to another (**13n**) in which the spirocycle **18n** was formed unexpectedly. The calculations indicated that the Gibbs energies for the transformation of **13e** to **14e** and (putative) **18e** (Scheme 7a) were both exergonic, but that indole **14e** is the thermodynamic product of the reaction ($\Delta G_{298} = -223$ kJ mol^{-1}) and spirocycle **18e** would be a kinetic product ($\Delta G_{298} = -58$ kJ mol^{-1}). Although employing the substituted pyrrole **13n** changed the outcome of the experimental reaction, it did not significantly alter this picture with **14n** being more stable than **18n**, indicating that this reaction is under kinetic control.

Silver(I) complexes are kinetically labile, and in the case of simple salts such as $AgNO_3$ the precise nature of the active species is unclear. However, the reaction of AgOTf with 1 equiv of PPh_3 results in the formation of known complex $Ag(OTf)(PPh_3)$.[22] It was anticipated that the ynone substrate would displace the weakly bound OTf ligand in this complex

Scheme 7. DFT-Calculated Energies for (a) the Formation of Compounds 14e/n and 18e/n from 13e/n and (b) Silver-Catalyzed C−C Bond Formation from Alkyne Complex A[a]



[a]Energies are Gibbs energies at 298 K at the D3-PBE0/def2-TZVPP//BP86/SVP(P) level with COSMO solvent correction in CH_2Cl_2 in kJ mol^{-1}.

to give a cationic silver(I) phosphine species that (1) would promote C−C bond formation and (2) could be effectively modeled by DFT. To demonstrate the feasibility of this approach, AgOTf (10 mol %) was mixed with PPh_3 (10 mol %) in CH_2Cl_2 solution to generate $Ag(OTf)(PPh_3)$. Subsequent reaction with **13e** for 3 h resulted in the formation of **14e** in 77% isolated yield, demonstrating that this was indeed a viable catalyst system.

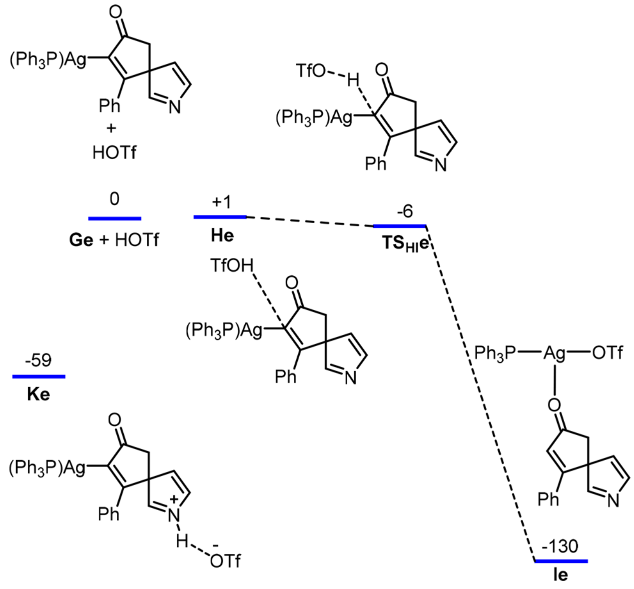
Therefore, the cyclization of ynones **13e** and **13n** was modeled by DFT using $[Ag(PPh_3)]^+$ as the catalyst system. The silver complex **A**, in which the alkyne is bound through the ynone oxygen atom, was taken as the reference state for the calculations (Scheme 7b). In the case of the cyclization reaction from **13e**, the η^2-(CC) bound alkyne complex **Be** lies at +2 kJ mol^{-1}, but C−C bond formation takes places from the slipped alkyne complex **Ce**, which may be viewed as being a formal carbocation. Two transition states for C−C bond formation were located. Transition state $\mathbf{ts_{CD}}$ is best viewed as nucleophilic attack by the C-3 atom of the pyrrole at the carbocation of **C** and leads to the silver-coordinated spirocycle **De**. A second transition state, $\mathbf{ts_{CE}}$, was also located, which corresponds to C−C bond formation between the C-2 position of the pyrrole with the carbocation leading to **Ee**, and subsequent keto−enol tautomerization would then give **Fe**.

On the basis of these calculations, the potential energy surface is almost flat, with $\mathbf{ts_{CD}}$**e** and $\mathbf{ts_{CE}}$**e** at +18 and +28 kJ mol^{-1}, respectively. Although the formation of **De** will occur more rapidly than **Ee** based on these data, the equilibrium position between **Ae**, **Be**, **Ce**, and **De** is expected to favor **Ae**. Therefore, as **Ee** is of significantly lower energy (−32 kJ mol^{-1}), this would be the expected product from the reaction, as long as protodemetalation is slow. All attempts to find a transition state connecting **De** and **Ee** (i.e., a formal 1,2-migration) resulted in $\mathbf{ts_{CD}}$.[23]

In the case of **13n**, the situation is somewhat different, as the corresponding complex **Dn** is now lower in energy than **An**, **Bn**,[24] and **Cn**. This may provide an explanation for the different reaction outcome in this case, as, in contrast to **13e**, the complex **Dn** will dominate the equilibrium between the states **A**−**D** (i.e., it will be the major resting state prior to the slower formation of **En**) and hence should be more prone to protodemetalation to give the spirocyclic product **18n**. This is consistent with **18n** being a kinetic product formed from the lower lying transition state ($\mathbf{ts_{CD}}$).

Examination of the predicted structure of **De** revealed that there are no elemental intramolecular steps that could lead to protodemetalation. Therefore, this step must involve an intermolecular deprotonation/protonation pathway; however, modeling such steps is fraught with difficulty as the precise nature of the base is unclear. To obtain at least an indicative picture of this process, triflate was used as a model base. The neutral metalated spirocycle **Ge** and triflic acid were used as the reference point for the calculation (Scheme 8).

Scheme 8. DFT-Calculated Energies for Proton Transfer Reactions for Metalated Spirocycle[a]



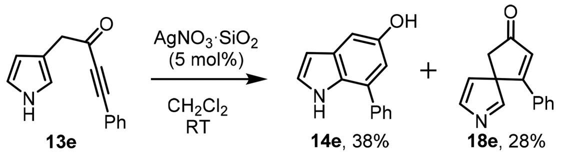
[a] Energies are Gibbs energies at 298 K at the D3-PBE0/def2-TZVPP//BP86/SVP(P) level with COSMO solvent correction in CH_2Cl_2 in kJ mol^{-1}.

Protodemetalation proceeds via an initial encounter complex **He** in which the HOTf has a weak interaction with the M−C bond. Proton transfer through $\mathbf{TS_{HI}e}$ is essentially barrierless,[25] implying that protonation of the Ag−C bond by HOTf is rapid. Protonation ultimately leads to **Ie**, which has a T-shaped geometry with the silver coordinated to PPh_3, a triflate anion, and an *O*-bound spirocycle.

A further state, **Ke**, was also located, which corresponds to **De** with a hydrogen bonded triflate anion. This is significantly lower in energy than both the reference state and those involved in proton transfer. These data imply that the rate of the proton transfer reaction would be controlled by the deprotonation of **De** rather than the protonation of the M−C bond, at least in the case of HOTf.[26]

Interestingly, the DFT results suggest that dearomatization through the pyrrole C-3 position (**C** to **D**) is lower in energy than dearomatization through the pyrrole C-2 position (**C** to **E**) in both ynone systems **13e** and **13n** (and, indeed, this is likely to be the case for most/all of the related ynones **13** in this study), but spirocyclic products are generally not isolated due to slow protodemetalation of the vinyl silver intermediate **D**. On the basis of this hypothesis, we reasoned that if the rate of protodemetalation of **D** could be increased relative to isomerization to **E**, this might enable C-3 spirocyclic products to be prepared by trapping intermediate **D**. To test this, we first attempted the reaction of ynone **13e** at lower temperature (0 °C), but this resulted in no reaction. Instead, the same reaction was then attempted using 5 mol % of the silica supported catalyst ($AgNO_3{\cdot}SiO_2$) in place of $AgNO_3$ at rt; $AgNO_3{\cdot}SiO_2$ was found to accelerate protodemetalation in our earlier work on related indole spirocyclization reactions, and hence we predicted that the use of this catalyst might enable spirocyclic vinyl silver intermediate **De** to be trapped out prior to rearrangement.[10d] Pleasingly, this experiment worked well; although the use of $AgNO_3{\cdot}SiO_2$ did not lead to a complete switch in chemoselectivity, spirocycle **18e** was indeed formed, and isolated in 28% yield, alongside indole **14e**, which was formed in 38% yield (Scheme 9).[27] These results add strong support to those obtained in the DFT study that spirocyclic vinyl silver species **De** is an intermediate in the synthesis of indole **14e**, and also show that under appropriate conditions, this intermediate can be intercepted, enabling synthetically challenging C-3 spirocyclic pyrrole derivatives to be prepared.

Scheme 9. Synthesis of Spirocycle 18e



In summary, a new "back-to-front" method to generate substituted indoles from pyrrole ynol and ynone precursors has been developed. The synthetic procedures are promoted by relatively mild silver(I) catalysts, proceed at room temperature, and are insensitive to air and moisture. DFT studies conducted on the pyrrole-tethered ynone series (**13**) suggest that these reactions proceed via nucleophilic attack onto the activated alkyne via the pyrrole C-3 position, going against the generally accepted view that pyrroles are most nucleophilic through C-2. Formal C-2 annulation products are still formed in most cases (likely via ring opening and reclosing), but this discovery could be highly significant in the design of new dearomatizing spirocyclization methods for pyrrole precursors; methods to prepare C-3 spirocycles from pyrroles are very rare, but the knowledge that they are transiently formed en route to C-2 annulated products should help to inform new strategies by which the spirocycles can be intercepted prior to rearrangement.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acscatal.8b00745.

> Full characterization data, images of NMR spectra and experimental and computational details for all of the materials produced in this study, as well as a link to the raw data (PDF)

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Notes

The authors declare no competing financial interest.

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(26) A transition state connecting **Ke** and **De** + HOTf could not be located.

(27) As was found for spirocycles **18n** and **18o**, spirocycle **18e** does not rearrange when resubjected to the reaction conditions (with both $AgNO_3$ and $AgNO_3{\cdot}SiO_2$) or upon reflux in CH_2Cl_2.